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Cook NR, Rosner BA, Hankinson SE, Colditz GA. Mammographic screening and risk factors for breast cancer. American Journal of Epidemiology. 2009 Dec;170(11):1422-32. doi: 10.1093/aje/kwp304.

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ACKNOWLEDGEMENT

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After 20 Years of Treatment with Aprepitant for Chemotherapy-Induced Nausea and Vomiting, Should the Therapeutic Indications for Aprepitant be Expanded?

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The drug aprepitant, a selective antagonist of the neurokinin-1 receptor (NK-1R), was approved in 2004 by the FDA for the treatment of CINV, blocking the activation of the receptor by substance P (SP). Oral aprepitant (day 1: 125 mg; days 2-3: 80 mg) (low doses) was coadministered with dexamethasone and a serotonin 5-HT3 receptor antagonist. The aprepitant triple regimen is effective for the prevention of CINV in patients being treated with moderately or highly emetogenic chemotherapy [1]. Furthermore, activation of the SP/NK-1R system has been reported to mediate also pruritus and cough. A study published on 17 patients with skin T-cell lymphomas (CTCL) with refractory pruritus was treated with aprepitant administered according to the standard of 125–80–80 mg either in a weekly or a biweekly repetition regimen. They show that aprepitant was safe, well tolerated and effective for the treatment of severe chronic pruritus in patients with CTCL [2]. In addition, two randomized clinical trials have clearly demonstrated that aprepitant (day 1: 125 mg; 2-7/2-3: 80 mg) suppresses treatment-refractory cough in patients with lung cancer [3,4]. Regarding safety, NK-1R antagonist aprepitant was safe and well tolerated. In a placebo-controlled trial in patients with moderate-to-severe major depression, a dose of 300 mg/day (moderate doses) of aprepitant was well tolerated and no statistically significant difference in the frequency of adverse events was observed as compared with placebo. Additionally, aprepitant was as antidepressant as paroxetine [5]. Furthermore, in the las 20 years has been reported many papers about the involvement of SP/NK-1R in cancer progression and the use of NK-1R antagonist aprepitant counteract all the pathophysiological functions of SP related to cancer. In fact, aprepitant is a broad-spectrum antitumor drug. Obviously, the concentrations or doses of aprepitant to have antitumor activity are higher (20-40 mg/kg/day) (high doses) [6].

In conclusion, based on the safety (low and moderate doses) and efficacy of aprepitant, its use in refractory pruritus with CTCL and treatment-refractory cough in patients with lung cancer should be approved. Regarding cancer treatment (high doses) we suggest the initiation of a Phase I clinical trial to see what safe doses are and Phase II clinical trials to evaluate the efficacy of aprepitant alone or in combination therapy with chemotherapy or radiotherapy at least in tumors with the poor prognosis.

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Original Article

Prevalence of Inflammatory Back Pain (IBP) In Patients with Backache Visiting Rheumatology OPD at Khyber Teaching Hospital, Peshawar

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ABSTRACT

Back pain is a prevalent and often paralyzing condition that impacts people of all ages and backgrounds. When it comes to back pain, it is crucial to differentiate between different kinds in order to accurately diagnose and effectively treat the problem. **Objective:** To ascertain the frequency of Inflammatory Back Pain (IBP) in patients presenting with low back pain. **Methods:** This descriptive study was conducted in rheumatology department of Khyber Teaching Hospital, Peshawar, during the period 1st September 2023 till 31st March 2024. Male and female patients with back ache (VAS >4) were enrolled and evaluated for the presence of inflammatory back pain using ASAS criteria. **Results:** The study included 138 patients, 60 (43.48%) male and 78 (56.52%) female. Mean age was 51.7 ± 5.8 years. Majority of the patients belonged to the age group 46 to 60 years 45 (32.60%). The ASAS criteria for IBP was satisfied by 54 (39.1%) patients. Statistically significant association was observed between IBP and family history of IBP. **Conclusions:** Significant proportion of patients with back pain were found having pain with inflammatory etiology. Male patients aging 46 to 60 years with family history of IBP were more likely having IBP.

INTRODUCTION

Back pain is a prevalent and often crippling condition that impacts people of all ages and backgrounds with socio-financial implications [1, 2]. When it comes to back pain, it is crucial to differentiate between different kinds in order to accurately diagnose and effectively treat the underlying etiology [3, 4]. IBP is a distinct type of back pain that is characterized by particular traits, including morning stiffness, relief with activity, and discomfort at night [5]. The identification of IBP is especially important since it might suggest the presence of underlying inflammatory diseases like Ankylosing Spondylitis (AS) [6]. Inflammatory or rheumatic condition like ankylosing spondylitis affects the axial skeleton, causing inflammation in the lumbosacral and iliac joints [7]. The timely detection and treatment have been linked to better long-term results and preventing long term complications [8, 9]. The ASAS has created criteria to assist in the categorization of IBP, hence promoting uniform methods for its recognition [10]. Comprehending the prevalence of IBP in certain healthcare environments might provide significant knowledge about the impact of inflammatory back pain on a specific population [11, 12]. The Rheumatology OPD at KTH treats a wide patient group. The local epidemiology of inflammatory back pain and the early diagnosis and treatment of potentially significant underlying diseases may be improved by studying IBP prevalence in this scenario.

This study evaluated the prevalence of IBP and associated clinical features in backache patients at KTH's

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Rheumatology OPD to better understand the burden of inflammatory back pain in our population and improve diagnostic strategies and patient outcomes.

METHODS

This descriptive study was carried during the period 1st September 2023 till 31st March 2024, in the Rheumatology Outpatient Department (OPD) at Khyber Teaching Hospital, Peshawar and a tertiary care hospital that caters to a wide range of patients. A total of 138 patients were registered who presented with a symptom of backache. Sample size was calculated using WHO sample size calculator taking 6.7% anticipated prevalence of IBP, with 5% margin of error and 95% confidence level [12]. Male and female patients in the age range 18 to 70 years complaining of back pain (VAS>4) were enrolled. Previously labelled IBP, history of lumbar surgery, patients with bone calcification disorder and patients with metastatic bone disease were excluded. Before recruitment in the research, each participant provided informed consent. Permission for the conduct of the study was granted by hospital research review committee vide letter no: 21/DME/KMC, dated: 10/8/2023. Each participant's demographic data, including age, gender, and pertinent medical history, were documented. Patients were assessed by experienced rheumatologist to determine the existence of IBP using the Assessment of SpondyloArthritis International Society (ASAS) criteria. ASAS criteria was considered positive for the presence of inflammatory back pain when any 4 of the following features were present: (a) morning stiffness > 30 min; (b) age of onset <40 years (c) no improvement by rest (d) awakening because of the pain in the second half of the night only (e) alternating buttock pain and (f) duration of back pain. The study explicitly examined key characteristics, including morning stiffness, enhancement via physical activity and discomfort experienced throughout the night. Relevant laboratory tests were performed to evaluate inflammatory indicators, such as Erythrocyte Sedimentation Rate (ESR) and C-Reactive Protein (CRP). ESR more than 15mm/hr for male and more than 20mm/hr for female was considered raised while CRP more than 1.0mg/dl was considered high. The purpose of these tests was to provide evidence for the clinical evaluation of IBP. Presence of both clinical symptoms and raised inflammatory markers was considered confirmatory for the presence IBP. Data were collected using statistical analysis program SPSS version 25.0. Means and standard deviation was computed for continuous data like age, ESR and CRP and frequencies and percentages were recorded for categorical data like gender, residence, education, profession, family history and inflammatory back pain. Inflammatory back pain was stratified by age, gender, BMI, residence, education, profession and family history to control the effect modifiers. Post stratification chi square test was applied. P value ≤0.05 was considered statistically significant.

RESULTS

As illustrated in table 1, out of the total 138, male participants were 60 (43.48%). The mean age was 51.7 years with standard deviation 5.8. Majority of the participants were in the age group 46-60 years comprising of 45 individuals accounting for 32.60% of the total.

Table 1: Demographics of Study Participants (n = 138)

Variables	N (%)
Gender	
Male	60 (43.48%)
Female	78 (56.52%)
Age Group (Years)	
18-30 Years	25 (18.12%)
31-45 Years	40 (28.99%)
46-60 Years	45 (32.60%)
61 And Above	28 (20.29%)
Mean Age (Mean ± SD)	51.7 ± 5.8

Morning stiffness was reported by 78 (56.5%) patients. 92 (66.7%) patients reported pain relief with exercise and nocturnal pain 64 (46.4%) as shown in table 2.

Table 2: Distribution of Patients with Respect to Symptomatology (n = 138)

Back Pain Features	N (%)
Morning Stiffness	78 (56.5%)
Improvement with Exercise	92 (66.7%)
Nocturnal Pain	64 (46.4%)

The mean erythrocyte sedimentation rate was 23.4 ± 8.1 mm/1st hour while the mean CRP was 12.7 ± 4.5 mg/dl as shown in table 3.

Table 3: Laboratory Findings in Study Participants

Laboratory Investigations	Mean ± SD
Erythrocyte Sedimentation Rate (ESR)	23.4 ± 8.1
C-reactive Protein (CRP)	12.7 ± 4.5

Inflammatory back pain was observed in 54 patients (39.1%) as reported in table 4.

Table 4: Frequency and Percentage of Patients According to Inflammatory Back Pain Based on Assessment of Spondylo-Arthritis International Society (ASAS) Criteria, (n = 138)

Inflammatory Back Pain	N (%)
Yes (ASAS Satisfied)	54 (39.1%)
No (ASAS Not Satisfied)	84 (60.9%)

Table 5 reported subgroup analysis of IBP with various clinico-demographics parameters. The number of male participants with IBP were 30 (50.0%) while IBP positive female patients were 24 (30.8%). The p-value for association between gender and presence of IBP was 0.021. Inflammatory back pain was most commonly observed in the age group 46 to 60 years, however, this

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distribution was statistically not significant, p-value 0.190. 31 patients (36.5%) with IBP belonged to urban areas. Majority of the patients with inflammatory back pain were having normal BMI 21 (46.7%) while no statistically significant association was demonstrated between the presence of IBP and education of the patient p-value 0.379. With respect to profession, most of the participants 22 (51.2%) were not actively attached to any profession. The association between the presence of IBP and family history of IBP was statistically significant (p-value <0.001).

Table 5: Subgroup Analysis of Patients with IBP with Respect to Various Clinico-Demographic Parameters, (n = 138)

Variables	Subgroups	Inflammatory Back Pain		Total	p-Value
		Yes N (%)	No N (%)	N (%)	
Gender	Male	30 (50.0%)	30 (50.0%)	60 (100%)	0.021
	Female	24 (30.8%)	54 (69.2%)	78 (100%)	
Age (Years)	18-30 Years	10 (40.0%)	15 (60.0%)	25 (100%)	0.190
	31-45 Years	18 (45.0%)	22 (55.0%)	40 (100%)	
	46-60 Years	22 (48.9%)	23 (51.1%)	45 (100%)	
	61 And Above	04 (14.3%)	24 (85.7%)	28 (100%)	
Residence	Urban	31 (36.5%)	54 (63.5%)	85 (100%)	0.508
	Rural	23 (43.4%)	40 (56.6%)	53 (100%)	
BMI (Kg/m^2)	<18.5 Kg/m^2	09 (60.0%)	06 (40.0%)	15 (100%)	0.162
	18.5-23.9 Kg/m^2	21 (46.7%)	24 (53.3%)	45 (100%)	
	24.0-29.9 Kg/m^2	17 (42.5%)	23 (57.5%)	40 (100%)	
	>30.0 Kg/m^2	07 (18.4%)	31 (81.6%)	38 (100%)	
Education	Primary	13 (65.0%)	07 (35.0%)	20 (100%)	0.379
	Secondary	15 (31.2%)	33 (68.8%)	48 (100%)	
	Tertiary	26 (37.1%)	44 (62.9%)	70 (100%)	
Profession	Office Job	19 (44.2%)	24 (55.8%)	43 (100%)	0.057
	Manual Labor	13 (25.0%)	39 (75.0%)	52 (100%)	
	Sedentary	22 (51.2%)	21 (48.8%)	43 (100%)	
Family History	Yes	14 (20.0%)	28 (41.2%)	70 (100%)	<0.001
	No	40 (58.8%)	28 (41.2%)	68 (100%)	

DISCUSSION

The prevalence of IBP in patients seeking evaluation for pain localized to lumbosacral region of the back, in our study was 39.1%. In an earlier research on the prevalence of IBP carried out by Rudwaleit M and Sieper J showed that 57.0% of patients were found low back pain which was inflammatory in nature [13]. This proportion is greater than our observation. This difference may be attributed to more stringent criteria for patient enrollment in the later study where patients with low back pain and additional symptoms like morning stiffness and relief with exercise were also considered. Similar findings were reported by Bittar M *et al.*, in their study our study are however similar to the results of the study by Sieper J *et al.*, in 2009 who reported 40.0% patients with IBP among patients presenting with low back pain [14, 15]. Poddubnyy D *et al.*, demonstrated that 38% of patients with low back pain had IBP [16]. The laboratory results in this investigation, particularly the average ESR and CRP readings, are in agreement with earlier research by Rusman T *et al.*, the average Erythrocyte Sedimentation Rate (ESR) was found to be 22.5 and the average C-reactive Protein (CRP) level was 11.5 in patients with Inflammatory Back Pain (IBP) [17]. Similarly, another study reported an average ESR of 24.5 and an average CRP level of 12.8 in patients with Ankylosing Spondylitis (AS). The proportion of IBP in male patients was slightly greater than females in this study, is in coherence with earlier studies. A study discovered that patients with IBP had a male to female ratio of 2.3:1 [19]. Another study indicated a male to female ratio of 3.2:1 in patients with inflammatory conditions like ankylosing spondylitis [20]. The increased incidence of IBP in the 46-60 age bracket seen in this study aligns with findings from earlier research Rudwaleit M and Sieper J identified the greatest incidence of IBP among individuals aged 40-49 years [13]. The association between BMI and IBP found in this study is also supported by previous research. A higher BMI has been linked to an increased risk of developing IBP, as excess weight can put added stress on the spine and lead to degenerative changes [21]. The high proportion of patients with a family history of IBP in this study is also in line with previous studies, which have shown a genetic predisposition to the condition, highlighting the importance of screening and early intervention for individuals with a family history of IBP [21]. The research comprised of a small size and included people from one center, limiting its generalizability. The research did not include a control group, making it impossible to compare IBP prevalence in the studied population to the general population. Finally, the research used self-reported symptoms without objective assessments, which may have influenced outcomes.

CONCLUSIONS

A significant proportion of patients presenting with low back pain were found in inflammatory back pain. Morning stiffness and exercise improvement were common in patients with IBP. Inflammatory back pain is more common in male patients aging 45 to 60 years. No significant association was observed between the presence of IBP and sociodemographic parameters of the patients, however, the association with family history of IBP was statistically significant.

Authors Contribution

Conceptualization: AA
Methodology: N, AZ, I, IK
Formal analysis: N, AZ
Writing, review and editing: AA, N, AZ, I, IK

All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Failure Factors of Medical Students in Private and Public Sector Medical Colleges of Peshawar, Khyber Pakhtunkhwa

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ABSTRACT

In the medical world, stress and anxiety are very communal to manage educational affairs. Motivation is a failure among medical students is a very crucial point of discussion. **Objective:** To find factors that led to failure of medical students in public and private sector medical colleges. **Methods:** Qualitative approach was adopted for this cross-sectional study. Fourteen in depth interviews were carried out. Purposive sampling was implemented for this study that included medical students who failed in any one year of their medical journey, of public and private sector medical colleges in Peshawar. **Results:** Out of total interviewed participants, 64% of the respondents were female while 36% of the respondents were males. Amongst the total respondents, 71% were from private medical colleges whereas, 29% were from public medical colleges. 79% of respondents wanted to continue with same profession whereas 21% of respondents did not wanted to continue with their medical profession. Three main factors were observed that lead towards failure of medical students in public and private medical colleges. These factors include lack of peer support, instructor's teaching attitude and pressure from institute and family. **Conclusions:** This study identified lack of peer support, instructors' teaching attitude, and pressure from the institute and family as primary factors leading to the failure of medical students in public and private colleges in Peshawar. Despite these challenges, 79% of students remain motivated to continue their medical careers.

INTRODUCTION

Stress and anxiety are communal to manage educational affairs in medical world. Persistent engagement in activities and practical's bound medical students to achieve their educational goals and worry about their future in medical world. Study pressure, result worry and tension of failure results in student poor performance and ultimately failure in examination. Keeping this entire situation in mind, key purpose of this study is to focus on strengths of medical students such as motivation after failure in both public and private sector medical colleges of Peshawar. The inverse relations between failure and success make medical students more involved in situation to revise their skills and identify weak points through self-assessment [1]. This increases student's strengths and motivates students to decrease chances of failure in public and private medical colleges in future. However, it is pertinent to discuss that most medical students struggle to find motivation after failure in public and private medical colleges. Their attitude, behavior and approach to find motivation to bounce back become less desirable for them. In this regard, this study focused to explore how strengths of these medical students remain in cage [2]. For medical students, failure in both public and private medical colleges is a nightmare considering social, moral and psychological implications. Social and moral implications makes medical student less resistant to this unwanted tragedy [3].

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Student's psychological condition also turns into a complete blackout. Their resistance against this mental blockade becomes very hard.

This study focused on factors that cause medical students to fail in their exams in public and private medical colleges.

METHODS

This study was conducted from 24th February to 25th August 2023. In the start, to carry the research approval from the Advance Studies and Research Board (ASRB) (ASRB001457/ES/IHPE) was taken at 29/07/2021. Also, permission was taken from the Khyber Medical University (KMU) to initiate the data collection procedure. Informed consent was obtained from all participants prior to data collection. Qualitative approach was used to explore strengths and motivation in medical students of public and private medical colleagues in Peshawar. This research study used Brannan research protocols which mentioned that qualitative research study provides researchers with deeper insight of issues [4]. These issues can become subjective because data derived in qualitative research study is based on experiences, opinions and thoughts [5]. Moreover, a qualitative approach is more efficient in finding social issues that require a large number of data. This type of study also allows researcher to perceive responses differently by focusing on subjectivity of collected data instead of objectivity [1]. Key reason behind non-probability purposive sampling as a sampling method is the research objectives, as researcher cannot include all students of all colleges or medical colleges. Therefore, inclusion criteria was set to include medical students of public and private medical colleges in Peshawar who failed in at least anyone year of their medical journey. Use of this technique allowed researcher to be relevant in participant's selection. Interviewing selected medical students was main data collection method to answer research questions that was thought suitable to explore motivation after failure. Fourteen participants were interviewed to explore the research questions, generate information such as new themes and in-depth knowledge about research questions [5]. To avoid missing any fundamentals of the research a task based systematized data collection procedure was used to ensure that all tasks were completed within allotted time [6].

RESULTS

Amongst the total respondents 10 (71%) were from private medical colleges whereas, 4 (29%) were from public medical colleges, as shown in figure 1.

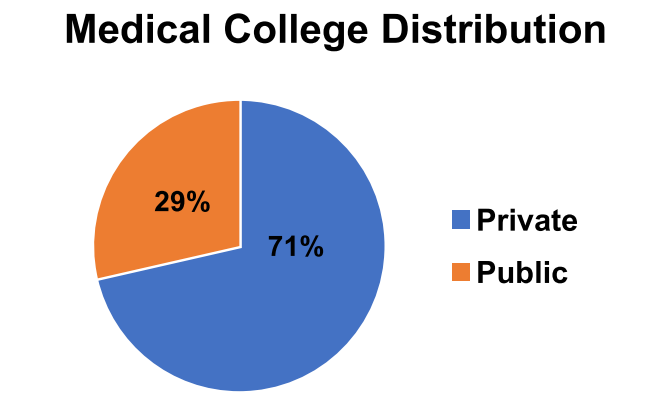

Figure 1: Distribution of Participants Based on Medical College

During conduction of analysis it was reflected that students failed their exams because of lack of peer support, teaching attitude of instructors and too much pressure from institute and family, as shown in figure 2.

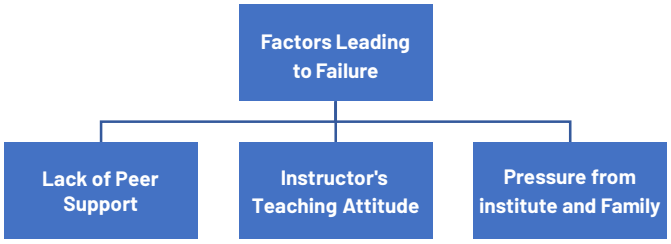

Figure 2: Factors Leading to Failure of Medical Students

Failure does not impact the ambition of medical students as they are still motivated towards learning skills, clearing exam and endeavoring for better in their carrier. In the current survey among all interviewed participants 79% of respondents wanted to continue with same profession where as 21% of respondents did not want to continue with their medical profession, as shown in figure 3.

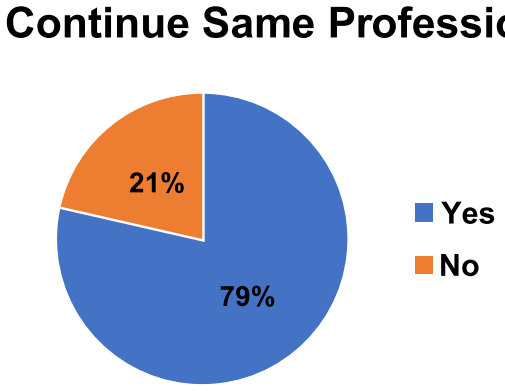

Figure 3: Chart Showing Percentage of Continuation of Same Profession after Failure

Various factors have emerged after conducting analysis for positives gained after failure, as shown in figure 4.

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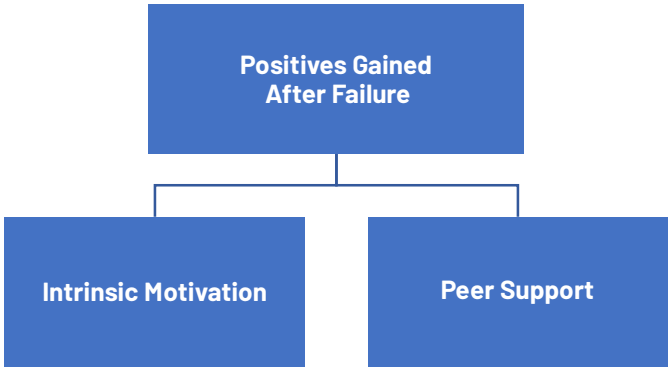

Figure 4: Positives Gained After Failure

DISCUSSION

Our study emphasizes the critical role of peer support in medical education, highlighting that the absence of this support poses significant challenges for students. More precisely, 71% of our respondents came from private medical schools, where there was very little peer support. This result supports the work of Graves J *et al.*, in 2022, who also stressed the value of social connections among medical students for group study peer support and empowerment [7]. Strong peer interactions were associated with a 20% greater test pass rate in students than in those without such support, according to Graves J *et al.*, which is consistent with our findings that group study increased motivation and performance. In a similar vein, Abrams MP *et al.*, in 2022 suggested peer-support initiatives to improve the medical student community and came to the conclusion that peer support provides medical students with translational skills useful for their residency and professional responsibilities [8]. Our discovery that a key contributing reason to student failure was a lack of peer support is supported by the 75% of participants in their survey who said that peer support helped them acquire practical skills. Teacher-student relationship have changed as medical education has moved toward self-directed, student centered learning. In our survey, 64% of women and 36% of men said that their dedication and morale were greatly impacted by the attitude of their teachers. This is supported by Mercer C in 2018, who reports that the little availability of doctors for supervision made it impossible for 70% of medical students in their studies to get necessary information outside of lectures [9]. This outcome is consistent with our finding that, when asking for assistance outside of class, many students felt abandoned. Schiekirka-Schwake *et al.*, in 2017, further emphasized how the absence of open data on medical school instructors distorts the quality of instruction and makes it more difficult for students to learn. It is consistent with our finding that students often lacked the help and explanations they needed from teachers because 60% of them believed that insufficient instructional support hampered their academic achievement [10]. Findings from our study revealed that institutional and familial pressures significantly contribute to medical students' exam failures. Students face recurring pressure, often comparing their performance to that of older family members, which exacerbates their stress and hinders their ability to succeed. Enhancing family dynamics and fostering greater cooperation with medical students have been shown to have a positive impact on their overall well-being and academic performance [11]. Driven by expectations from their families and their academics, medical students often have serious concerns about their mental health. According to our survey, 21% of participants did not want to continue in their field while 79% did. This is consistent with the findings of Bergmann C *et al.*, in 2019, who found that the demands of their families and their studies caused significant levels of stress in 65% of medical students [12]. In keeping with our discovery that family pressure is a major factor in student failure, Hussain A *et al.*, also reported that 68% of students felt that high parental expectations negatively affected their academic and personal life [13]. Strong intrinsic motivation was shown by the large majority 79% of students who are still driven to pursue their medical professions in spite of the obstacles. According to Hussain A *et al.*, changing words like "failed" to "not yet" may greatly increase student motivation and morale. Our finding of intrinsic motivation among students after failure is supported by their research, which found that 85% of students felt more driven after positive reinforcement [13]. During clinical rotations in particular, Sarkis AS *et al.*, in 2020 found that autonomous motivation motivates students to continue their studies even after setbacks. Their result that 80% of students who interacted with patients during rotations felt more motivated is consistent with our discovery that 79% of students maintained their motivation in the face of academic failures [14, 15]. Good things that come of failing include more inner drive and peer support. In a study of Failure, Panja A pointed out, results in a stronger resolve and the formation of encouraging peer ties [16]. It was found that peer support is essential to academic resilience, which is consistent with this. According to Hayat AA *et al.*, students who received emotional support after a setback were 30% more motivated, which improved their academic feelings and performance going forward [17]. Failure often provokes suspicious hopes that diminish the inspiration which in turn causes further challenges. Not only that but, failure habitually persuades contemplation and contributes in self-exhaustion and depression that causes hindrance with their work and achievements [18]. Data of certain studies on failure as well successful students revealed that it is quite difficult to determine aspects on overall medical field. They consider the tendency for medical

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undergraduates to assume as compound learning strategies as superficial, deep and strategic [19]. This supports the fact that 79% of students were still driven to pursue medical jobs. Recent studies have further emphasized these points. For instance, a study on the state of clinical education by BMC Medical Education in 2023 reported that the personal characteristics of students and instructors significantly impact clinical education effectiveness. The study highlighted that instructor performance and student interaction was rated at average levels, stressing the need for better educational planning and evaluation. Another study on academic burnout by BMC Medical Education in 2023 found that a substantial percentage of students experience academic burnout, influenced by demographic factors such as gender, parental education, and living expenses. These studies underscore the multifaceted challenges medical students face, reaffirming the importance of supportive educational environments and mental health resources [20].

CONCLUSIONS

This study identified three primary factors contributing to the failure of medical students in both public and private medical colleges in Peshawar: lack of peer support, the teaching attitude of instructors, and pressure from the institute and family. Despite these challenges, the majority of students 79% expressed a desire to continue pursuing their medical careers, indicating a strong level of resilience and motivation. These findings highlight critical areas that need attention to support medical students and reduce failure rates.

Authors Contribution

Conceptualization: MK
Methodology: MK, AZ, UA
Formal analysis: PS, TS
Writing, review and editing: MK, PS, AZ, SH, TS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Disease Patterns of Ankylosing Spondylitis Associated Treatment Patterns and Drug Utilization among Affected Patients

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ABSTRACT

Ankylosing Spondylitis is disease with significant morbidity. With biological DMARDs, treatment is revolutionized compared to conventional options. The article will discuss disease pattern, risk factors and treatment response of various drugs on this disease. **Objective:** To evaluate the prevalence, risk factors, treatment patterns, and drug utilization associated with Ankylosing Spondylitis (AS) among patients in clinical practice. **Methods:** This prospective cross-sectional study was done at territory care hospital in Rawalpindi from June 23 to December 23. Data comprised of methods to identify AS, particular tests used to verify diagnosis, numerical and clinical traits of patients included. Study also peruse percentage of patients identified as HLA-B27 positive, Time elapsed between initial symptom appearance and clinical diagnosis of AS, satisfaction of classification criteria and treatment strategies employed, such as advanced therapies for controlling AS disease activity. **Results:** Mean values for current disease occurrences and functional index outcomes were 3.3 ± 2.1 and 1.8 ± 1.09 in the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Bath Ankylosing Spondylitis Functional Index (BASFI) were used, respectively. Patients in study received treatment with adalimumab (43%) and Infliximab (27%) for an average period of 3.1 ± 2.1 years. Treatment satisfaction showed convenience domain had lowest score (4.2), whereas scores for side effects, effectiveness, and global satisfaction were 93.7, 75.41, and 73.81, respectively. **Conclusions:** Among bDMARDS adalimumab was most administered followed by Infliximab. Better therapeutics have improved patient satisfaction. Research revealed a significant decrease in productivity as a result of AS.

INTRODUCTION

Ankylosing Spondylitis (AS) is one of the chronic autoimmune disease primarily affecting the axial skeleton, leading to prolonged and debilitating illness [1]. It is characterized by the presence of fomenting and gruesome back pain, which ultimately results in structural and functional impediment and a less in overall standard of life. Males exhibit a higher prevalence rate compared to females, with a mean ratio of 3.4 to 1 [2]. Around 80% of individuals experience the initial symptoms of AS before reaching the age of 30, whereas less than 5% of people manifest symptoms after the age of 45 [3]. Due to the compromised physiological functioning experienced by individuals diagnosed with AS, the disease exerts a substantial impact on occupational circumstances. Individuals diagnosed with AS exhibit impairments in various occupational domains, including uninterrupted work performance, prolonged standing, ambulation, sustained focus, interpersonal interactions and productivity in terms of both quantity and quality, as well as adherence to deadlines. The aforementioned constraints lead to a reduction of production by 6.3% as compared to individuals in good health or alternatively, an increase in working hours by 7.1% [4]. Given the absence of a cure for AS, the primary objective of treatment approaches

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revolves around managing symptoms, mitigating joint deterioration, and attaining or sustaining disease remission [5]. Commonly used therapeutic options include non-steroidal anti-inflammatory drugs (NSAIDs), Disease-Modifying Antirheumatic Drugs (DMARDs), and newer biological DMARDs. NSAIDs are often recommended as the initial treatment to manage pain and stiffness [4]. In cases where NSAIDs prove to be ineffective, the use of bDMARDs is advocated [6]. This recommendation is supported by significant evidence indicating a prompt and lasting response, particularly in younger patients with a brief duration of the disease, elevated levels of inflammatory indicators, and favorable functional grade [7]. Several biologics, such as adalimumab, secukinumab, infliximab, and ixekizumab, have received approval for the management of AS in patients who have not shown a satisfactory response to NSAIDs. The diagnosis and management of AS involve the involvement of many specialists, such as rheumatologists and orthopedists, who may adopt distinct therapeutic approaches [1].

This study aimed to investigate the frequency, risk factors of Ankylosing Spondylitis (AS) its corresponding treatment strategies and medication usage among those affected patients within the context of clinical practice.

METHODS

After the ethical approval from institutional review board, via Letter ID A/28/ER/17/23, this prospective cross-sectional study was conducted at Territory Care Hospital Rawalpindi from June 2023 to December 2023. Through non-probability consecutive sampling, 200 participants above age 19 years, presenting the symptoms of AS of either gender were incorporated in the present study. Sample size was calculated using WHO calculator, Confidence interval was 95% and margin of error was 5%. The prevalence of Ankylosing Spondylitis (AS) was 0.32% [8]. Patients less than 19 years of age, have any other connective tissue co-morbidity were excluded from the present study. The collected data encompassed various aspects related to the diagnosis of Ankylosing Spondylitis (AS) by physicians. This encompassed their methodology for diagnosing AS, the particular tests and evaluations used to validate the diagnosis and The study examined the statistical and patient related characteristics. It also analyzed the proportion of patients who tested positive for HLA-B27 and the duration linking initial clinical signs and Ankylosing Spondylitis diagnosis, the satisfaction of classification criteria and the treatment strategies employed, such as advanced therapies for controlling disease activity in Ankylosing Spondylitis. The study also evaluated the onus of disease reported by patients with AS, using validated criteria. Participants were asked to voluntarily take part in doing various standard evaluations to determine disease progression, general wellbeing status, the study assessed the Quality of Life (QoL) and productivity of participants. It analyzed the demographic and clinical characteristics of the study patients, as well as their treatment approaches. Descriptive statistics were used to present treatment satisfaction (TSQM) and productivity loss, including percentages for definite data and mean with standard deviation for numerical data. The data of the study was analyzed in SPSS version 20.0.

RESULTS

Table 1 presented the demographic characteristics of the 200 study participants recruited for the study. Mean age of the participants was 52.34 ± 12.32 years, with 67% were males, the average BMI was 25.2 ± 3.5 kg/m^2, mean time span of disease was 6.4 ± 3.2 years. About 51% of the participants have secondary school education, and 79% were breadwinning.

Table 1: Demographic Parameters of the Study Participants (N=200)

Variables	N (%)/(Mean ± SD)
Age (Years)	52.34 ± 12.32
Male	134 (67%)
Females	66 (33)
Education (Secondary School or Less)	102 (51%)
Education (College or More)	98 (49%)
Employment Status (Employed)	157 (79)
Employment Status (Unemployed)	43 (22)
BMI (Kg/m^2)	25.2 ± 3.5
Duration of Disease (Years)	6.4 ± 3.2
Comorbidity (Yes)	58 (29%)
BASFI	1.8 ± 1.09
BASDAI	3.3 ± 2.1
Injection Pain, VAS	2 ± 2.12

In table 2, the mean values for current disease progress and functional index scores were reported as 3.3 ± 2.1 and 1.8 ± 1.09 in the Bath Ankylosing Spondylitis Functional Index (BASFI) and Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), respectively. The individuals in the study had received treatment with any Tumour Necrosis Factor Inhibitor (TNFi) for an average period of 3.1 ± 2.1 years. At the time of study enrolment, adalimumab (43%) and Infliximab (27%) were the most frequently utilized TNFi among the four evaluated in this investigation. The current TNFi were administered for an average duration of 5.0 ± 1.3 years of adalimumab and 5.3 ± 2.4 years for etanercept. A significant number of patients (37%) had been maintained on a low dose, defined as below the permitted dose, in the year preceding their enrolment in the study. In comparison to the other TNFi, adalimumab was administered at a lower dosage in the majority of patients. Approximately 49% of the participants with TNFi were given a pen-type device being spoken for subcutaneous injection, as shown in table 2. In relation to concurrent therapies, 26% of the patients utilized conventional disease-modifying antirheumatic medications (cDMARDs), 72% employed NSAIDs, and 26%

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utilized steroids. In the examination of treatment satisfaction, it was observed that the convenience domain had the lowest score (4.2), whereas the scores for side effects, effectiveness, and global satisfaction were 93.7, 75.41, and 73.81, respectively.

Table 2: Disease Pattern of the Study Participants (N=200)

Disease Pattern	N=200 N (%)/(Mean ± SD)
TNFi Therapy From Initiation (Years)	3.1 ± 2.1
Current TNFi Treatments	
Infliximab	54 (27%)
Etanercept	40 (20%)
Adalimumab	85 (43%)
Golimumab	20 (10%)
Duration of Current TNFi Medication in Years	
Infliximab	4.3 ± 2.1
Etanercept	5.3 ± 2.4
Adalimumab	5.0 ± 1.3
Golimumab	3.2 ± 1.9
Doses of the Current TNFi Therapy Administered in the Past Year Per Admission	
Approved	127 (63%)
Low	73 (37%)
Infliximab	
>6 mg	20 (37%)
<6 mg	34 (63%)
Adalimumab	
<40 mg	60 (71%)
>40 mg	25 (29%)
Etanercept	
<50 mg	25 (63%)
>50 mg	15(37%)
Golimumab	
<50 mg	2 (10%)
>50 mg	18 (90%)
BASDAI Score Categorized by Treatment and Dosage	
Approved	3.2 ± 2.3
Stunted	3.4 ± 1.7
Infliximab	
>6 mg	3.3 ± 1.8
<6 mg	2.9 ± 1.5
Etanercept	
>40 mg	3 ± 1.9
>40 mg	3.7 ± 2.1
Golimumab	
<50 mg	3.1 ± 1.2
>50 mg	2.8 ± 1.4
BASDAI Score Categorized by Treatment and Dosage	
Approved	1.6 ± 1.2
Stunted	1.5 ± 1.9
Infliximab	
>6 mg	2 ± 2.2
<6 mg	1.3 ± 1.9
Adalimumab	
>40 mg	1.7 ± 1.8
>40 mg	1.5 ± 1.6
Etanercept	
<50 mg	2.3 ± 1.8
>50 mg	2.5 ± 1.2
Golimumab	
<50 mg	2.1 ± 1.2
>50 mg	1.3 ± 1.3
Approach of Device Type Bespoken	
Subcutaneous Syringe	54 (27%)
Intravenous	48 (24%)
Subcutaneous Pen	98 (49%)
Accompanying Use Of DMARD (Yes)	39 (20%)
Concomitant Use Of NSAID (Yes)	143 (72%)
Auxiliary Use Of Steroids (Yes)	52 (26%)

Table 3 represented the productivity loss of the study participants with AS. The loss of productive hours being more than total absence from duty. Partial absence from job is also slightly higher than total absence. Productivity loss from disease has also significant financial burden as shown in the table 3.

Table 3: Productivity Loss of Patients with AS (N = 200)

Productivity Loss of Patients	Mean ± SD
Days exerted if not sick with as during the last four weeks	24.5 ± 6.2
Number of full days absent from work in the last 4 weeks	1.2 ± 2.3
Partial absences on work days in the last 4 weeks (days); half-day absence	1.32 ± 2.6
Self-assessed job recital in the last 4 weeks	6.5 ± 1.5
Productive hours lost due to absenteeism In the last 4 weeks	5.9 ± 24.3
Productive time lost owing to reduced work Performance in the last 4 weeks (hours)	54.3 ± 32.2
Hours of lost productivity	55 ± 34.2
Yearly expense due to employee absenteeism In Pakistani rupees	449242 ± 65430
Yearly expenses due to presenteeism yearly Expenses due to lost productivity (pkr)	3368711 ± 45760
Yearly expenses due to lost productivity (pkr)	3817953 ± 132987

DISCUSSION

Ankylosing spondylitis (AS) is a chronic, inflammatory and debilitating disease mainly affecting the axial spine and manifest with myriad of clinical signs and symptoms. The hallmark features include chronic back pain and progressive spinal stiffness. AS is characterized by the involvement of the spine and sacroiliac (SI) joints and peripheral joints, digits, and entheses. Involvement of sacroiliac joint radiologically confirms the diagnosis of ankylosing spondylitis. AS effects any gender but it effects males more than females due to HLA-27 and complex genetic interaction between various genes. approximately 2:1 ratio [9]. In 2009–2010, the National Health and Nutrition Examination Survey estimated that the prevalence of axial

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AS among adults in the USA varies from 0.9 to 1.4%.[10] The number of AS cases in Europe and Asia is estimated to be 1.30–1.56 million and 4.63–4.98 million, respectively.[11] The onset of AS usually occurs before the age of 45 years[12] ,when adults are in their peak productive years, and patients experience limited physical function, significant loss of work productivity, and a decreased quality of life during this period after disease onset [13]. Thus AS is an important healthcare and socioeconomic issue. Various risk factors have been identified in pathogenesis of ankylosing spondylitis, recently role of gut microbiota is one of them and an area of extensive research. [14] A metagenomics study analyzed gut microbial DNA from 211 Chinese individuals and found that patients with AS had an increased load of *Prevotella melaninogenica, Prevotella copri*, and *Prevotella* sp. C561, and decreases in *Bacteroides* sp [15]. Furthermore, role of Klebsiella pneumoniae has also been implicated in pathogenesis of AS [16]. Cigarette smoking aswell as E-smoking has also been indentified as risk factor in progression of AS [17]. Patients in Pakistan with Ankylosing Spondylitis (AS) who underwent TNFi medication were the subjects of this prospective cross-sectional study, which sought to analyse treatment satisfaction, treatment pattern, and productivity loss. In addition, we investigated the related aspects that help us comprehend the entire disease burden that AS patients face and how TNFi might be practically applied to their treatment. The primary objective of treatment for AS is to mitigate symptoms, enhance and sustain spine flexibility and proper posture, minimize functional impairments, preserve occupational capacity, and mitigate the potential consequences associated with the condition [18]. The effectiveness of TNFi in treating AS has been extensively documented, and their utilization has become an integral part of clinical protocols [19]. Internationally, there exists variation in the utilization of TNFi medications across different countries, as no specific TNFi treatment is universally endorsed over its counterparts. The findings of this study indicate that adalimumab was the most commonly utilized TNFi among the four available options in Pakistan, with Infliximab being the subsequent choice in terms of usage frequency. Sweden and Brazil exhibit a somewhat similar pattern to Pakistan in terms of the frequency of prescribing adalimumab, but etanercept is more typically given in the United States and Canada [20, 21]. In the present investigation, it was observed that around 37% of the participants had been consistently prescribed a low dosage of their current TNFi for a duration of one year prior to their enrolment in the study. The disease activity exhibited by individuals receiving low-dose TNFi treatment were found to be comparable to those observed in patients receiving the recommended dosage of TNFi. Amid the TNFi assessed in this study, adalimumab, specifically, exhibited a longer duration of maintenance and was administered at a lower dosage for a greater percentage of patients. The observed inclination towards an extended duration of adalimumab utilization in the present investigation does not aligns with the findings of a prior study conducted in Korea, which demonstrated a prolonged persistence with etanercept as a second-line treatment option for TNFi [22]. This investigation noted the simultaneous use of a tumour necrosis factor inhibitor with traditional disease-modifying antirheumatic medications (cDMARDs) for the treatment of AS, despite the lack of data about the efficacy and safety of cDMARDs in this setting. The European League Against Rheumatism (EULAR) guidelines for the control of AS from 2016 suggest that patients with peripheral arthritis may benefit from this combination medication [23]. The study found that patient satisfaction with TNFi was much greater than to treatment gratification reported for other unabating diseases in Pakistan. It was observed that the convenience domain had the lowest score (4.2), whereas the scores for side effects, effectiveness, and global satisfaction were 93.7, 75.41, and 73.81, respectively. Based on the analysis of TSQM data obtained from prior research, it was observed that individuals diagnosed with postmenopausal osteoarthritis indicated their level of satisfaction with treatment in the dominion of effectiveness, adverse effects, expedience, and worldwide contentment as 56, 64, 63, and 54, respectively. Patients with irregular heart rate who received vitamin K treatment manifested their satisfaction scores as 58, and 56 in the corresponding TSQM domains. In this study, the domain of treatment convenience exhibited the lowest reported satisfaction among the four domains. In the present investigation, it was observed that individuals participating in the research work experienced a mean absence duration of 1.2 full days and 1.3 partial days throughout the preceding four-week period. The observations of this research was similar with those of a prior findings based on Korean employees, which documented an average of 5.22 hours of work absenteeism resulting from back or neck illnesses [24]. In many research investigations, the concept of productivity loss has been employed as a composite measure encompassing both absenteeism, denoting the act of being off-duty from work, and staying longer than usual, which pertains to the effectiveness of work performed by an individual. The reduction in yield is typically quantified as an annual expense and is referred to as an indirect cost [25]. Structured review and meta-synthesis have documented the costs associated with productivity loss in individuals diagnosed with AS. This comprehensive study identified a total of 32 records that specifically examined the issue of productivity loss in AS patients [25]. The study findings indicate that the yearly indirect expenses associated with reduced productivity in individuals with AS who are undergoing biologic treatment vary between 191 USD and 45,954 USD per individual, based on 2013 USD values [25]. Within the meta-analysis, a study was

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identified that documented a significant drop in indirect costs subsequent to treatment with a biologic medication. Specifically, the study saw a reduction from an initial value of 1968 USD to a post-treatment value of 191 USD [26]. In our investigation, the yearly expenditure associated with LPT amounted to 3817953 ± 132987PKR. This figure is within the spectrum of forgoing documented indirect costs in AS and is similar to the expenses incurred by patients in Korea diagnosed the costs associated with moderate and severe rheumatoid arthritis are 11,085 USD and 13,157 USD, respectively [27]. There are various limitations inherent in this study. Due to the utilization of a prospective cross-sectional study design in this study, the ability to investigate the correlation among factors and patients' reported satisfaction and depletion of productivity was limited. It is important to note that variability in comprehension and interpretation of each item among participants may have been introduced by the utilization of self-reported instruments in this study. Despite the precursory constraints, it is important to highlight the notable positives of this study. This study employed established and verified metrics that have been extensively utilized in previous research. Consequently, this study is a valuable point of reference for comparing results obtained in future studies using the same cohort of participants. Furthermore, this study aims to comprehensively examine the variations in treatment satisfaction, treatment patterns, and expenses associated with Decreased productivity observed in Ankylosing Spondylitis (AS) patients in Pakistan, so contributing to a deeper knowledge of these characteristics within the context of different countries.

CONCLUSIONS

After analysing the data, it was found that out of the four TNF inhibitors currently used to treat In Pakistan, adalimumab is the most commonly prescribed treatment for AS, followed by infliximab. Similar success in regulating disease activity has been seen with the continuous use of adalimumab, usually provided at a modest dose. It seems that adalimumab, even at reduced dosages, can be used in real-world clinical settings and may be sustainable. Among individuals diagnosed with AS, the current TNFi treatment was shown to be quite acceptable. Having said that, happiness was noticeably lower in the treatment convenience domain compared to the other three. Compared to subcutaneous pen injections, subcutaneous syringe and intravenous injections were associated with lower levels of satisfaction. Overall treatment satisfaction might be enhanced by making treatment options more accessible.

Authors Contribution

Conceptualization: MUR
Methodology: AK, HS, FFA, MHL, MFH
Formal analysis: FFA
Writing, review and editing: FFA, MHL, MFH, AN

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Exploring the Link between Obesity and Hypothyroidism

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ABSTRACT

The association between obesity and hypothyroidism has garnered significant attention due to their overlapping prevalence and potential bidirectional relationship. **Objectives:** To investigate the link between obesity and hypothyroidism in local population of Pakistan. **Methods:** A cross-sectional study conducted at Medical Unit DHQ Teaching Hospital in Dera Ismail Khan from 2022 to 2023 involved 550 participants. Demographic characteristics, age, gender, clinical parameters, body mass index (BMI), comorbidities, and thyroid blood tests (TSH, T4) were collected through systematically designed questionnaire. Lifestyle factors, dietary habits, physical activity and medication history were also recorded. Electronic medical records were reviewed to collect demographic information and medication history. **Results:** Data from 550 participants, meeting inclusion/ exclusion criteria, showed that individuals with hypothyroidism had a lower mean age (42.5 ± 8.6 years) than obese counterparts without hypothyroidism (45.2 ± 9.8 years). The odds ratio (OR) for the association between obesity and hypothyroidism was 2.45 (95% CI: 1.75 - 3.42), indicating a significant positive correlation ($p < 0.001$). Family history of thyroid disorders was present in 24.0% of individuals with subclinical hypothyroidism and 20.5% without. Mean BMI was higher in individuals with subclinical hypothyroidism (29.3 ± 3.5 kg/m2) than those without (27.8 ± 2.9 kg/m^2). **Conclusions:** Our study confirmed obesity's strong link to hypothyroidism, especially in females, stressing the need for thyroid evaluation in obese individuals, particularly in clinical settings.

INTRODUCTION

Increase in the morbidity of obesity and hypothyroidism gives rise to a critical problem considering their high coexistence and mutual influence. Obesity, which involves excessive fat gathered in contact, can be classified as a global risk and is a particular problem of metabolic complications [1]. Besides, hypothyroidism also stems from a deficit of thyroid hormones characterizing a metabolic slowdown that is eventually associated with weight gain. People need to comprehend the situation, as it is crucial both for managers and for measures being taken. There has been a recognition of obesity as a factor which worsens hypothyroidism, and in several studies, especially among obese patients, a higher prevalence of thyroid hormone in both was observed. [3]. Moreover, hypothyroidism has been linked to weight gains and having difficulty in losing weight, making the situation even more complicated for the pandemic of overweight [4]. The prevalence of thyroid disorders, encompassing thyroid dysfunctions and autoimmune thyroid diseases (AITDs), is on the rise. Thyroid dysfunctions, including hyperthyroidism and hypothyroidism, manifest in both subclinical and overt stages, with changes in thyroid-stimulating hormone (TSH) levels and thyroid hormones [5]. AITDs, among the most common autoimmune conditions, involve autoantibodies targeting thyroid antigens like TSH receptor antibody (TRAb), thyroid peroxidase antibody (TPOAb), and thyroglobulin antibody (TGAb) [6]. Moreover, thyroid patients are prone to extra illnesses such as cardiotoxicity, and cancer, obesity, and life-threatening widespread infections [7]. The patients

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with thyroid dysfunctions (or GD) frequently require long-term medical management or observation to help manage health outcomes. The purposing of factors of possible thyroid diseases by the doctors assists them in the proper detection and the intervention early on to make the end results of the patients good as well as to understand the physiological mechanism of diseases [8]. Currently, obesity is a prevalent global health concern, with escalating rates observed over recent decades. Associated with a myriad of health disturbances, including coronary heart disease, stroke, dyslipidemia, and Type II Diabetes Mellitus (TIIDM), obesity contributes significantly to adverse health outcomes, with excess weight contributing to a notable proportion of all-cause deaths among adults [9]. Especially crucial to address in children, subclinical hypothyroidism (SCH) may contribute to metabolic abnormalities and atherosclerosis [10]. Despite observations of a higher prevalence of SCH among obese individuals, inconsistencies exist in establishing a definitive link between obesity and SCH, with some studies failing to establish a significant association [11]. The presence of thyroid autoantibodies plays a pivotal role in the pathogenesis of SCH and influences thyroid hormone levels. Notably, obesity is implicated in the heightened risk of various autoimmune disorders, including autoimmune thyroiditis. Understanding the intricate interplay between obesity and SCH holds promise in informing preventive strategies and optimizing patient outcomes by addressing modifiable risk factors [12].

In this study, we aimed to find the link between obesity and hypothyroidism in local population of Pakistan.

METHODS

This cross-sectional study was conducted at Medical Unit, District Head Quarter Teaching Hospital, Dera Ismail Khan from 2022 to 2023. This study was designed to find the association between obesity and hypothyroidism. Data were collected from 550 participants. The study included participants aged 18 years and above diagnosed with obesity (BMI ≥ 30 kg/m^2) and hypothyroidism determined through clinical evaluation and specific thyroid function tests, including TSH and T4 levels. Exclusion criteria comprised individuals with prior thyroid disorders or surgeries related to the thyroid, as well as pregnant and lactating women. Data were collected from 550 participants according to inclusion and exclusion criteria. The sample size of 550 participants was determined using power analysis for logistic regression, considering factors like anticipated effect size, significance level, and desired statistical power. The sample size for this study was determined using power analysis for logistic regression, considering parameters such as the anticipated effect size (estimating the magnitude of the relationship between obesity and hypothyroidism), significance level (α) set at 0.05, statistical power (1-β) set at 0.80 or higher, and the number of predictor variables included in the logistic regression model. Demographic characteristics, gender, age, clinical parameters, and thyroid tests (TSH, T4) were obtained from the questionnaire. This data set also comprised of lifestyle factors, dietary habits, level of activity, and medication history which was collected as well. Medical records from the hospital were analyzed to get age, sex, and medication history information. 5cc of blood were used to be as patient's lab investigations, which we were subjected to centrifugation of the blood samples at 4000rpm for 15min in order to derive serum. Keep the serum in -80ºC for further laboratory diagnostic purposes. Thyroid function tests, including serum levels of thyroxin-stimulating hormone (TSH) and free T4 and triodithronine (T3) are crucial for hypothyroidism diagnosing were performed. Lipid profile was the obesity measurement criterion as well. Descriptive statistics were used for demographic and clinical characteristics of the study population by using SPSS 29.0. Logistic regression was applied to assess the association between obesity and hypothyroidism because the dependent variable (hypothyroidism) is binary. Binary logistic regression was used, with hypothyroidism (presence or absence) as the dependent variable. Independent variables included BMI (to represent obesity), TSH levels, free T4 levels, age, gender, lifestyle factors (such as dietary habits and level of activity), and medication history. This method allowed for the evaluation of how these variables influence the likelihood of having hypothyroidism while controlling for potential confounders.

The study received ethical approval from the Institutional Review Board (IRB) of Medical Unit DHQ Teaching Hospital, Dera Ismail Khan. Approval was granted on 16-12-2022, with reference number [267/GJMS/JC]. Informed consent was obtained from all individual participants included in the study.

RESULTS

Data were collected from 550 participants by considering inclusion and exclusion criteria. Those with hypothyroidism exhibited a lower mean age (42.5 ± 8.6 years) compared to obese counterparts without hypothyroidism (45.2 ± 9.8 years). Additionally, a higher proportion of females (55.8%) was observed in the hypothyroidism group compared to males (44.2%). Comorbidities such as diabetes and hypertension were more prevalent in the hypothyroidism group, with prevalence rates of 20.9% and 27.9%, respectively. Notably, medication use, particularly levothyroxine (91.7%) and metformin (18.6%), was higher among individuals with hypothyroidism. The lifestyle factors among the study participants showed that 54.2% of those without hypothyroidism engaged in regular physical activity compared to 34.9% of those with hypothyroidism. A high-

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fat diet was reported by 33.3% of participants without hypothyroidism and 41.9% of those with hypothyroidism. A high-sugar diet was consumed by 29.2% of the non-hypothyroid group and 37.2% of the hypothyroid group. Regarding smoking, 25 participants without hypothyroidism smoked compared to 70 participants with hypothyroidism, while alcohol consumption was noted in 15 participants without hypothyroidism versus 35 participants with hypothyroidism (table 1).

Table 1: Demographic and Clinical Characteristics of Participants

Characteristics	Obese without Hypothyroidism (n=120)	Obese with Hypothyroidism (n=430)
	Frequency (%)	
Age (years)		
Mean ± SD	45.2 ± 9.8	42.5 ± 8.6
Gender		
Female	80 (66.7%)	240 (55.8%)
Male	40 (33.3%)	190 (44.2%)
Socioeconomic Status		
Middle class	90 (75.0%)	320 (74.4%)
Lower class	30 (25.0%)	110 (25.6%)
Body Mass Index (BMI)	31.6 ± 3.4	30.2 ± 2.8
Comorbidities		
Diabetes	35 (29.2%)	90 (20.9%)
Hypertension	45 (37.5%)	120 (27.9%)
Medication Use		
Levothyroxine	110 (91.7%)	-
Metformin	30 (25.0%)	80 (18.6%)
Lifestyle Factors		
Regular Physical Activity (%)	65 (54.2%)	150 (34.9%)
High-Fat Diet (%)	40 (33.3%)	180 (41.9%)
High-Sugar Diet (%)	35 (29.2%)	160 (37.2%)
Smoking (Yes/No)	25/95	70/360
Alcohol Consumption (Yes/No)	15/105	35/395

Elevated levels of Thyroid-Stimulating Hormone (TSH) were noted (9.6 ± 3.2 mIU/L; reference range: 0.4 - 4.0 mIU/L), accompanied by decreased Free Thyroxine (T4) levels (table 2). Furthermore, participants displayed elevated Total Cholesterol (220 ± 30 mg/dL), LDL Cholesterol (140 ± 20 mg/dL), Triglycerides (180 ± 25 mg/dL), Fasting Blood Glucose (110 ± 15 mg/dL), and C - Reactive protein (5.0 ± 2.0 mg/L) levels, whereas, HDL Cholesterol (50 ± 10 mg/dL) levels were within the desired range.

Table 2: Blood Parameters and Lipid Profile in Hypothyroidism Group

Blood Parameter	Hypothyroidism Group (n=430)	Reference Range
Thyroid-Stimulating Hormone (TSH) (mIU/L)	9.6 ± 3.2	0.4 - 4.0
Free Thyroxine (T4) (ng/dL)	0.8 ± 0.2	0.8 - 1.8
Total Cholesterol (mg/dL)	220 ± 30	< 200
LDL (mg/dL)	140 ± 20	< 100
HDL (mg/dL)	50 ± 10	> 40
Triglycerides (mg/dL)	180 ± 25	< 150
Fasting Blood Glucose (mg/dL)	110 ± 15	70 – 100
C-Reactive Protein (mg/L)	5.0 ± 2.0	< 3.0

Among individuals below 30 years, a higher percentage of females were diagnosed with overt hypothyroidism (8.9%) compared to males (4.0%), with a significant difference observed (p = 0.123). In contrast, among participants aged 30 years and above, Females had a significantly greater incidence of overt hypothyroidism (28.2%) than men (16.7%) in Table 3, even if statistical significance was not reached (p = 0.456).

Table 3: Prevalence of Thyroid Status by Age Group and Gender

Age group	Gender	Thyroid Status	Percentage (%)	p-Value
Below 30 Years	Male	Overt Hypothyroid	4.0	0.123
		Subclinical Hypothyroid	0.7	
		Euthyroid	9.8	
	Female	Overt Hypothyroid	8.9	
		Subclinical Hypothyroid	0.9	
		Euthyroid	30.9	
30 Years and Above	Male	Overt Hypothyroid	16.7	0.456
		Subclinical Hypothyroid	16.9	
		Euthyroid	54.7	
	Female	Overt Hypothyroid	28.2	
		Subclinical Hypothyroid	20.9	
		Euthyroid	71.1	

The presence of a family history of thyroid disorders was observed in 24.0% of individuals with subclinical hypothyroidism and 31.5% of those without subclinical hypothyroidism (table 4). The mean BMI was higher in individuals with subclinical hypothyroidism (29.3 ± 3.5 kg/m2) compared to those without. Table 4 demonstrates the higher rates of smoking (15.4%) and alcohol consumption (10.4%) among individuals with subclinical hypothyroidism in comparison to those without the condition (13.2% and 8.8%, respectively), suggesting possible lifestyle factors linked to thyroid dysfunction.

Table 4: Risk Factors and Lifestyle Habits in Subclinical Hypothyroidism Group

Blood Parameter	Subclinical Hypothyroidism (n=208)	Non-Subclinical Hypothyroidism (n=222)	Total (n=430)
Family History	50 (24.0%)	70 (31.5%)	120 (27.90%)
BMI (kg/m^2)	29.3 ± 3.5	27.8 ± 2.9	28.5 ± 3.2
Smoking (Yes/No)	30/178	40/202	70/380
Alcohol Consumption (Yes/No)	20/188	30/192	50/380

Table 5 presents the distribution of obesity classes among 550 participants, categorized by the presence or absence of subclinical hypothyroidism. In the subclinical hypothyroidism group, 40.9% were classified as Class I obesity (BMI 30.0 - 34.9 kg/m^2), 36.1% as Class II obesity (BMI 35.0 - 39.9 kg/m^2), and 23.1% as Class III obesity (BMI ≥ 40.0 kg/m^2). Similarly, in the non-subclinical hypothyroidism group, 42.4% were classified as Class I obesity, 35.1% as Class II obesity, and 22.5% as Class III obesity. These

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findings highlight the distribution of obesity classes within each subgroup, showing a slightly higher prevalence of Class I obesity in both groups.

Table 5: Distribution of Obesity Classes among Participants with and without Subclinical Hypothyroidism

Classes of Obesity	Subclinical Hypothyroidism (n=208)	Non-Subclinical Hypothyroidism (n=342)	Total (n=550)
Class I (BMI 30.0 - 34.9 kg/m^2)	85 (40.9%)	145 (42.4%)	230 (41.8%)
Class II (BMI 35.0 - 39.9 kg/m^2)	75 (36.1%)	120 (35.1%)	195 (35.5%)
Class III (BMI ≥ 40.0 kg/m^2)	48 (23.1%)	77 (22.5%)	125 (22.7%)

A positive correlation was found between TSH levels and BMI ($r = 0.21$, $p = 0.003$), indicating that higher TSH levels were associated with increased BMI values (table 6). Conversely, Free T4 levels showed a negative correlation with BMI ($r = -0.15$, $p = 0.021$). Total T3 levels did not show a significant correlation with BMI ($p = 0.178$). There is a substantial positive connection ($p < 0.001$) between the chance of having hypothyroidism and obesity. The odds ratio (OR) for this relationship was 2.45 (95% CI: 1.75 - 3.42).

Table 06: Correlation between Thyroid Hormone Levels and BMI

Variable	BMI (kg/m^2)	Correlation Coefficient (r)	p-value
TSH (mIU/L)	28.5 ± 3.2	0.21	0.003
Free T4 (ng/dL)	28.5 ± 3.2	-0.15	0.021
Total T3 (ng/dL)	28.5 ± 3.2	0.08	0.178
Obesity and Hypothyroidism	-	1.75 - 3.42	<0.001

DISCUSSION

Our study delved into the intricate relationship between obesity and hypothyroidism, shedding light on their interplay within the local population of Pakistan. Our study findings corroborate previous research indicating a significant positive correlation between obesity and hypothyroidism. In line with existing literature, our results showed that individuals with hypothyroidism had a lower mean age (42.5 ± 8.6 years) compared to obese counterparts without hypothyroidism (45.2 ± 9.8 years) [13, 14]. This reaffirms the idea that obesity may contribute to the development or exacerbation of thyroid dysfunction, potentially through mechanisms such as altered thyroid hormone metabolism or immune system dysregulation [15]. Our study observed a higher prevalence of thyroid disorders among individuals with a family history of thyroid dysfunction. Specifically, 24.0% of individuals with subclinical hypothyroidism had a family history of thyroid disorders compared to 20.5% of those without subclinical hypothyroidism [16]. Bosma *et al.*, found that screening based on fT4 instead of TSH decreased reflex testing from 23.8% to 11.2%. The positive predictive value (PPV) for clinical hypothyroidism increased from 17.3% to 52.2% [17]. The negative predictive value was 96.1% with TSH-based screening versus 97.8% with fT4-based screening and indicate that screening for thyroid dysfunction in older individuals in primary care can be enhanced by utilizing fT4 instead of TSH or by modifying the TSH cutoff value, offering potential cost reductions and improved diagnostic accuracy. A family history of thyroid disorders may predispose individuals to a higher risk of developing hypothyroidism, emphasizing the importance of considering genetic factors in thyroid disease assessment and management. Regarding thyroid function parameters, our results indicated elevated TSH levels and decreased Free T4 levels in individuals with hypothyroidism, consistent with the findings by Deshmukh *et al.*, and Yalmiz *et al* [18, 19]. Specifically, the mean TSH level was 9.6 ± 3.2 mIU/L, while the mean Free T4 level was 0.8 ± 0.2 ng/dL in the hypothyroidism group [20]. The positive correlation between TSH levels and BMI, with a correlation coefficient of 0.21 ($p = 0.003$), suggests that obesity may be associated with higher TSH levels, potentially reflecting thyroid dysfunction in obese individuals [21]. Conversely, the negative correlation between Free T4 levels and BMI implies that obesity may be linked to lower levels of free thyroxine. Our study found a correlation coefficient of -0.15 ($p = 0.021$) between Free T4 levels and BMI, indicating a modest inverse relationship [22]. This highlights the complex interplay between obesity and thyroid function, with obesity potentially influencing thyroid hormone levels through various physiological mechanisms.

CONCLUSIONS

Our study confirms a significant association between obesity and hypothyroidism, particularly prominent among females. The findings underscore the importance of thyroid function evaluation in obese individuals, especially within clinical settings. Notably, individuals with obesity exhibit a 2.45 times higher likelihood of hypothyroidism compared to non-obese counterparts. These results emphasize the imperative for early detection and management of thyroid disorders, particularly in the context of obesity.

Authors Contribution

Conceptualization: SK, NK
Methodology: SK, MZ, NURS, NK
Formal analysis: AR, MZ, NURS
Writing-review and editing: SK, AR, MZ, NURS, NK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Effectiveness of Endoscopic Sinus Surgery for Chronic Rhinosinusitis with Nasal Polyps: Follow-Up on Nasal Obstruction and Recurrence Rates

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ABSTRACT

Chronic rhinosinusitis with nasal polyps is a significant health issue linked with considerable morbidity and reduced life quality. Endoscopic Sinus Surgery (ESS) is a broadly accepted technique for nasal polyp's treatment. **Objective:** To assess and compare nasal obstruction in chronic rhinosinusitis patients with nasal polyps pre and post-ESS and to evaluate recurrence rates at 3rd and 6th month post-surgery. **Methods:** The study was conducted as an observational study at Lahore General Hospital ENT Department from June 2019 to June 2020. A total of 88 patients underwent ESS after medical assessment. Nasal obstruction was evaluated using a visual analog scale during follow-up at 2nd week, 3rd month and 6th month. Data were analyzed using SPSS 24.0 with chi-square tests for categorical variables ($p<0.05$). **Results:** The mean age of patients was 31.45 ± 11.343 years. At 3rd month post-operative, 59.1% had no nasal obstruction, while 34.1% had mild obstruction. At 6th month, 54.5% had no obstruction, and 37.5% had mild obstruction. Recurrence rates were 25% at 3rd month and 29.5% at 6th month. **Conclusions:** Higher nasal obstruction and recurrence rates were noted at 6th month compared to 3rd month post-ESS, highlighting the need for long-term follow-up.

INTRODUCTION

Chronic rhinosinusitis denotes persistent inflammation affecting the nasal passages and paranasal sinuses, persisting for a duration exceeding 12 weeks, affecting about 0.5-4.5% of the general population, therefore it poses a substantial economic burden on healthcare systems and significantly affects the quality of life of affected patients [1, 2]. It presents as congestion or blockage of nose, nasal discharge, hyposmia, post-nasal drip, pressure or pain in face. Additional symptoms may involve mucopurulent secretions and nasal polyps mainly in the middle meatus; CT-scan findings indicative of sinus involvement along with mucosal changes in osteomeatal complex [3]. Chronic Rhinosinusitis (CRS) is further divided into 2 subtypes based on the findings of nasal endoscopy, CRS with nasal polyps (CRSwNP) and CRS without nasal polyps (CRSsNP) [4]. Chronic Rhinosinusitis (CRS) arises from multitude of factors, including infectious agents (viral, bacterial and fungal), cystic fibrosis, immunodeficiency, allergies, ciliary dyskinesia, asthma, reflux, mechanical obstructions (deviated septum) and adenoid hypertrophy [5]. Sinonasal Polyposis (SNP) has a prevalence rate of 4% within the general population and higher occurrence of 25-30% among individuals diagnosed with chronic rhinosinusitis [6]. SNP causes blockage of

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nose, reduced sense of smell (hyposmia or anosmia) and a diminished quality of life [7]. Underscoring the medical importance of identifying, evaluating, and treating the condition [8]. The diagnosis of CRSwNP relies on medical history, clinical examination including anterior rhinoscopy, endoscopic examination, histopathology and radiological assessments [9]. CRSwNP treatment involves both medical and surgical approaches, both methods are employed to alleviate nasal obstruction, enhance sinus drainage, restore olfactory function and address any other indications of rhinitis [10]. Medical treatment involves corticosteroids, antimicrobials, antihistamines, decongestants, anti-leukotrienes, mast cell stabilizers, immunotherapy and environmental factors reduction. Corticosteroids, whether systemic or topical, are the only proven medical intervention for CRSwNP [9]. Presently, the Endoscopic Sinus Surgery (ESS) is widely acknowledged as an efficient treatment for Nasal Polyps (NP) [11, 12]. Hence, endoscopic sinus surgery focuses on the osteomeatal complex, addressing affected air cells, mucosal contact areas, and stenotic clefts. It also restores drainage and ventilation of frontal and maxillary sinuses through natural pathways. Systemic or topical steroids are generally effective for mild to moderate cases of nasal polyps. In cases where patients do not respond to medical therapy, surgery is often necessary, followed by post-operative topical nasal steroids to reduce recurrence [13]. ESS has significantly positive outcomes for CRSwNP [14]. In the diagnostic phase, nasal obstruction is the most predominant complaint in CRSwNP by the patients approximately 96.5% [15]. However, there is significant improvement in this symptom following surgery [16]. The study seeks to determine the effectiveness of endoscopic sinus surgery in CRSwNP, specifically examining changes in nasal obstruction and recurrence of polyps over the 3rd month and 6th month follow-up intervals. By following up these patients will guide us about future strategy (for how long and how frequent we have to follow up) to reduce the recurrence rate.

The study aimed to evaluate the effectiveness of ESS in CRSwNP, specifically examining changes in nasal obstruction and recurrence rates over the 3rd month and 6th month follow-up intervals. This will guide future strategies to reduce recurrence rates.

METHODS

This observational study was conducted in the department of ENT at Lahore General Hospital, Lahore / Postgraduate Medical Institute, Lahore, over a period of 12 months from June 2019 to June 2020. The study population comprised patients visiting Lahore General Hospital Lahore. A total of 88 patients with chronic rhinosinusitis with nasal polyps (CRSwNP) were selected for the study. The sample size was calculated by the following formula keeping the margin of error equal to 10% and level of significance equal to 5%.

$$n = \frac{Z^2_{1-\frac{\alpha}{2}} P(1-P)}{d^2}$$

P: Expected recurrence of nasal polyposis 6th month after ESS = 35% [17]
d^2: Margin of error = 10%
Z 1-α/2: Desired level of significance = 95%
N: Calculated sample size = 88 [18]

Non-probability purposive sampling was employed. Inclusion criteria encompassed clinically examined patients with nasal polyps of both genders, aged 15 to 70 years. Exclusion criteria included patients with intracranial extension confirmed by CT scan, patients with antrochoanal polyps confirmed by clinical assessment, patients with bleeding diathesis, patients with other co-morbidities (hypertension, diabetes, ischemic heart disease), patients unwilling to participate, and those not fit for surgery. A proforma was prepared and finalized. After obtaining complete history, general physical examination, ENT examination, nasal endoscopy and CT scan of the nose and paranasal sinuses were advised to assess the anatomy and extent of the disease. Informed consent was obtained, and participants were admitted to the ENT ward for surgery. Nasal obstruction was evaluated using a Visual Analog Scale (VAS), where patients rated their nasal patency on a scale from 0 to 10, with 0 indicating no obstruction and 10 indicating complete obstruction. This assessment was done prior to surgery and then during follow-ups at the 2nd week, 3rd month and 6th month post-surgery. Endoscopic sinus surgery was performed under general anesthesia using a standard anterior to posterior approach. Surgical steps were tailored based on the extent of the disease in each case. BIPP paste-soaked gauze was used as post-operative nasal packs, which were removed on the first post-operative day. All patients were prescribed post-operative antibiotics, intra-nasal and oral steroids, along with careful nasal debridement/toilet. Augmentin (co-amoxiclav) was administered at 50 mg/kg Three Times Daily (TDS), along with prednisolone at 1 mg/kg per 24 hours, for 5 days. Topical nasal steroids were advised twice daily for one month. Post-operative follow-up was conducted at the 2nd week, 3rd month and 6th month. At each follow-up, nasal obstruction was recorded using the VAS, where patients rated their nasal patency on a scale from 0 to 10. Nasal endoscopy was also performed at the 3rd and 6th month follow-up to assess the state of the mucous membrane of the nasal cavity and recurrence of the disease. Recurrence of nasal polyposis was considered when a nasal polyp reappeared in the nasal cavity within 3 months of follow-up. Data were entered and statistically analyzed using SPSS version 24.0. Quantitative data, such as age, were analyzed by calculating the mean and standard deviation, while qualitative data, including nasal

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obstruction and recurrence, were assessed by computing percentages. The chi-square test was utilized to evaluate associations and identify significant differences among categorical variables, with statistical significance defined as a p-value ≤ 0.05. The study was approved by the Institutional Review Board of Lahore General Hospital, Lahore (AMC/PGMI/LGH/Synopsis No/00104-19/Date/26-06-2019). Written consent was obtained from all participants and strict measures were taken to uphold privacy and confidentiality in accordance with the ethical guidelines set forth in the Helsinki Declaration of Bioethics.

RESULTS

The study encompassed of 88 patients diagnosed with chronic rhinosinusitis with nasal polyps. The patients were aged 15-70 years, with an average age of 31.45 ± 11.343 years, the gender distribution was notable, with 35 were males and 53 (60.2%) females. Pre-operatively, 9 (10.2%) patients had mild nasal obstruction, 28 (31.8%) had moderate obstruction and 51 (58.6%) had severe nasal obstruction. At 2nd week post-operatively, 10 (11.3%) patients had no obstruction, with 19 (21.6%) experiencing mild obstruction, 35 (39.8%) moderate obstruction, and 24 (27.3%) severe nasal obstruction. By the 3rd month follow-up, the proportion of patients with no obstruction increased to 52 (59.1%), while 30 (34.1%) had mild obstruction, 4 (4.5%) had moderate obstruction and 2 (2.3%) had severe obstruction. At 6th month post-operatively, 48 (54.5%) patients were free of obstruction, 33 (37.5%) had mild obstruction, 5 (5.7%) had moderate obstruction and 2 (2.3%) had severe obstruction as shown in table 1.

Table 1: Endoscopic Sinus Surgery Outcomes in Patients with CRSwNP Regarding Nasal Obstruction at 3rd and 6th Months Follow Up

Nasal Obstructions	Pre-Operative Follow-Up N (%)	Post-Operative Follow-Up N (%)		
		2nd Week	3rd Month	6th Month
No Obstruction	0%	10 (11.3%)	52 (59.1%)	48 (54.5%)
Mild	9 (10.2%)	19 (21.6%)	30 (34.1%)	33 (37.5%)
Moderate	28 (31.8%)	35 (39.8%)	4 (4.5%)	5 (5.7%)
Severe	51 (58.6%)	24 (27.3%)	2 (2.3%)	2 (2.3%)
Total	100%	100%	100%	100%

Similarly, among 88 patients, 22 (25.0%) had recurrence at 3rd month follow-up while majority 66 (75.0%) had no recurrence. Likewise among 88 patients, 26 (29.5%) had recurrence at 6th month follow-up while majority 62 (70.5%) had no recurrence as in shown in table 2.

Table 2: Endoscopic Sinus Surgery Outcomes in Patients with CRSwNP Regarding Recurrence at 3rd and 6th Months follow up

Recurrence	Follow-Up N (%)	
	3rd Month	6th Month
Yes	22 (25%)	26 (29.5%)
No	66 (75%)	62 (70.5%)
Total	100%	100 %

Among, 22 patients who had recurrence at 3rd month follow-up, 19 (21.6%) had recurrence and 3 (3.4%) had no recurrence at 6th month follow-up. Among 66 patients who had no recurrence at 3rd month follow-up, 7 (7.9%) had recurrence and 59 (67.1%) had no recurrence at 6th month follow-up as shown in table 3.

Table 3: Association Between Recurrence at 3rd Month and 6th Month Follow-Up

Recurrence at 6th Month Follow-Up N (%)	Recurrence at 3rd Month Follow-Up N (%)		Total N (%)	p-Value
	Yes	No		
Yes	19 (21.6%)	7 (7.9%)	26 (29.5%)	0.000
No	3 (3.4%)	59 (67.1%)	62 (70.5%)	
Total	22 (25.0%)	66 (75.0%)	88 (100.0%)	

DISCUSSION

Chronic sinus issues pose significant challenges for individuals, often leading them to seek frequent medical care from doctors and Ear, Nose and Throat (ENT) specialists due to profound impact in quality of life. Endoscopic sinus surgery is widely acknowledged as an effective treatment for chronic sinus issues along with nasal polyps. During this study nasal obstruction was evaluated pre and post-operatively. At the 3rd month follow-up, 59.1% of patients experienced relief from nasal obstruction, however this improvement slightly declined to 54.5% at 6th month post-surgical follow-up. Bosteels C and Dejonckheere S observed significant improvement in CRSwNP patients' obstruction of nose after surgery [19]. Similarly, Aslam S *et al.*, and Nair S *et al.*, showed higher improvements of 96% and 93% respectively in alleviating nasal obstruction after sixth month follow-up, further supporting the efficacy of endoscopic sinus surgery in treating CRSwNP [13, 6]. Recurrence remained the significant concern in our study following endoscopic sinus surgery, with rates ranging from 25.0% to 29.5% at three and six months follow-up respectively. However, Aslam S *et al.*, found lower recurrence rates of 6.0% at 3rd month and 6th month follow-up [13]. Similarly, Farrukh MS and Rafique M had 33% of the patients with recurrent disease [11]. A local study by Akhtar S *et al.*, had 19% recurrence rate at 14 months follow-up and Javaid W *et al.*, had 20% recurrence rate at 3rd week follow-up [20, 21]. DeConde AS *et al.*, work had slightly higher rates of recurrence about 40% following surgical intervention which contrasted significantly with Bosteels C and Dejonckheere S higher recurrence levels about 78.9% patients after surgery [17, 19]. Similarly, Calus L *et al.*, have found that 78.9% had recurrence after ESS and 36.8% had to undergo revision surgery [22]. Rest of the patients were managed with postoperative medications especially topical corticosteroids. Additionally, recent advancements in biologics show promise in preventing recurrence, suggesting potential improvements in future treatment protocols [23, 24]. These findings underscore the variability in recurrence rates post-ESS, highlighting

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the necessity for personalized treatment plans and the potential for integrating biologics to enhance long-term outcomes. Although, these studies highlight the recurrence of disease and nasal obstruction in postoperative ESS patients but only few emphases on both and with 6th month of follow-up period. Also there is limited local data available on it, which is covered by our study. This study provides insight about the effectiveness of ESS for treating CRSwNP, but it has limitations as small sample size, no control group and relatively short follow-up period. Future studies with larger samples and longer follow-up period is recommended.

CONCLUSIONS

Endoscopic Sinus Surgery (ESS) demonstrated significant improvement in nasal obstruction among postoperative patients. However, during follow-up recurrence of disease and nasal obstruction were more pronounced at 6th month compared to 3rd month postoperatively. These findings highlight the effectiveness of ESS as a management option for chronic rhinosinusitis with nasal polyps, underscoring the critical importance of long-term follow-up.

Authors Contribution

Conceptualization: AA
Methodology: MM, MSQ, BA
Formal analysis: UA, GDK, BA
Writing, review and editing: AA, UA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Knowledge Regarding Cervical Cancer Screening Among Medical and Non-Medical Undergraduates in Peshawar, Pakistan: A Step towards Preventive Healthcare

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ABSTRACT

A major global health concern, cervical cancer primarily affects younger women and those living in less developed areas. Comprehending students' knowledge, attitudes, and practices around cervical cancer screening is essential for future leadership roles in healthcare. **Objectives:** To assess the knowledge, attitude and practices regarding cervical cancer screening among undergraduate medical and non-medical students in Peshawar, Pakistan. **Methods:** A comparative observational cross-sectional study was conducted which lasted eight months. To accomplish a sample size of 474 through non-probability convenient sampling technique was used among undergraduate medical and non-medical students' population from Peshawar. A standardized questionnaire was used for data collection and SPSS version 26.0 was used for data analysis. **Results:** Among the participants, 62.9% acknowledged the significance of cervical screening in the early detection of lesions and 83.1% correctly identified HPV as the principal cause of cervical cancer. There was a general consensus toward early HPV screening (80.4%), and HPV vaccination (80.6%). However, there were clear differences in practice, 14.1% of participants reported smoking, 18.6% reported having pap smears, and 17.9% reported having had the HPV vaccine. **Conclusions:** The medical students were more knowledgeable about cervical cancer screening as compared to the non-medical. It was also concluded that even though the participants didn't participate in many preventive measures, most participants had positive attitudes towards early diagnosis, screening and HPV vaccination.

INTRODUCTION

Cervical cancer is highly preventable among humans and is predominantly found in females below the age of 45, with a notable prevalence among college-aged individuals [1]. Regional variations significantly affect the prevalence of cervical cancer; it is ranked fourth among women and seventh overall globally. Approximately 85% of cases are concentrated in less-developed areas, whereas it constitutes nearly 12% of all female cancer diagnoses [2]. The development of cervical cancer is strongly linked to Human Papillomavirus (HPV) infection, primarily type 16 and 18. Cervical cancer can be prevented through primary and secondary prevention. Preventing HPV infection constitutes the primary prevention, while cytological screening constitutes secondary prevention. According to the WHO, HPV's DNA detection screening should commence at age 30, followed by regular screenings every five to 10 years [3]. Epidemiological factors contributing to cervical cancer include engaging in sexual activity with

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multiple partners, starting sexual activity at a young age, contracting Human Papillomavirus (HPV) infection, experiencing lower genital tract neoplasia, being exposed to someone with cervical neoplasia, having a history of Sexually Transmitted Diseases (STDs), smoking cigarettes, being infected with Human Immunodeficiency Virus (HIV), experiencing other forms of immune system suppression, and long-term use of oral contraceptive pills [4-6]. Cervical cancer presents with symptoms such as irregular vaginal bleeding, pelvic discomfort, bleeding during or after sexual activity and abnormal vaginal discharge [7, 8]. It can be prevented by making efforts towards early detection of precancerous changes through cervical screening and also through administering HPV vaccines. However, numerous obstacles hinder cervical cancer screening particularly in developing nations like ours. This includes limited and underutilized screening resources, insufficient awareness and negative attitudes toward cervical cancer and its risk factors, cultural beliefs, a sense of well-being, social stigma, anxiety about test outcomes, and concerns about marital discord [8]. Research indicates that women with comprehensive knowledge and heightened awareness regarding cervical cancer are more inclined to participate in cervical cancer screening activities [9]. In 2013, Pakistan was ranked seventh in the Cervical Cancer Global Crisis Card for having one of the highest numbers of deaths from cervical cancer. The report stated that over 7,000 women succumb to this disease annually in the country [10]. Similarly, in another study from Lahore, Pakistan it was seen that 70.7% participants had poor knowledge, also 64% had a negative attitude towards cervical cancer screening [11]. After reviewing the literature on the burden of cervical cancer, there emerged a need to explore the knowledge regarding cervical cancer among both medical and non-medical students of Peshawar, Pakistan.

This research aimed to concentrate on students due to their role as future leaders and healthcare professionals, responsible for disseminating awareness about cervical cancer and screening. Assessing their knowledge, attitudes, and practices concerning cervical cancer was deemed essential for this purpose.

METHODS

The research was carried out in Peshawar, Khyber Pakhtunkhwa, Pakistan, using a comparative observational cross-sectional methodology. It was conducted from January 2023 to August 2023, for a total of eight months. By utilizing the Open Epi Sample Size Calculator, the sample size was calculated to be 471 participants with a 97% confidence level, a 5% confidence limit and a 51.6% anticipated frequency [12]. Students from medical and non-medical departments at multiple Peshawar institutions made up the study population. The research did not include those who voluntarily declined to participate. Prior to involvement, participants were informed of the objectives of the study and requested to provide informed verbal consent. Using the non-probability convenient sampling technique, a standardized questionnaire was employed to collect data. The questionnaire used for data collection was meticulously designed, drawing upon an extensive review of the existing literature and underwent validation by domain experts, resulting in a positive Cronbach's alpha value. Using in-person interviews, the questionnaires were distributed; 474 questionnaires were returned. The Northwest School of Medicine's Institutional Review Board and Ethics Committee approved the study's design (IRB&EC/2022-SM/054) (Issued Date: 12th September, 2022). The participant's knowledge of cervical screening prevention was assessed by assigning zero points for incorrect answers and 1 point for correct answers for all the knowledge, attitude and practice questions. The participants who had scored equal to or more than the median for correct responses were labelled as having adequate knowledge, positive attitude and good practices. While those with correct responses less than the median were labelled as having inadequate knowledge, negative attitude and poor practices [12]. The students from first and second year were grouped into junior years whereas the students from third, fourth and fifth year were grouped into senior years. The data analysis was done with SPSS version 26.0. To analyze the variables, descriptive statistics were used, such as means with standard deviation, frequencies, and percentages. With a significant P-value of 0.05 to identify any significant differences, the link between the responses of medical and non-medical students was examined using the chi-square test.

RESULTS

This study comprised 474 participants, with 264 enrolled in medical programs and 210 in non-medical programs. The average age of the participants was 21.42 years, with a standard deviation of 1.843, ranging from 17 to 27 years. Of the participants, 267 (56.3%) were in their junior years of study, while 207 (43.7%) were in their senior years. Among them, 30 (6.3%) were married, with 13 from the medical field and 17 from non-medical fields as shown in table 1.

Table 1: Demographic Characteristics of the Participants

Variables	Medical N (%)	Non-Medical N (%)	Total N (%)
Participants' Year of Study			
Junior Years	170 (63.7%)	97 (36.3%)	267 (100%)
Senior Years	94 (45.4%)	113 (54.6%)	207 (100%)
Participants' Marital Status			
Single	251 (56.5%)	193 (43.5%)	444 (100%)
Married	13 (43.4%)	17 (56.7%)	30 (100%)
Total	264 (55.7%)	210 (44.3%)	474 (100%)

The study participants were asked about their knowledge

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regarding cervical cancer and its screening. A large majority (83.1%) correctly identified Human Papillomavirus (HPV) as the primary cause of cervical cancer (p-Value = 0.000). Among the 474 participants, 166 (35%) were knowledgeable about the various strains of HPV (p-Value = 0.001). Of the participants, about 62.9% acknowledged that cervical screening helps identify precancerous lesions early on (p-Value = 0.055), and 73.4% thought that early identification helped prevent and treat cervical cancer (p-Value = 0.033). Moreover, 64.1% believed that precancerous lesions progress slowly to cervical cancer (p-Value = 0.523). The participants identified having multiple sexual partners as the most perceived risk factor (55.9%), followed by HPV infection (52.1%). Yet, increasing parity was the least perceived risk factor, cited by only 15% of the participants as shown in table 2.

Table 2: Knowledge of the Participants Regarding Cervical Cancer and its Screening

Variables	Medical N (%)	Non-Medical N (%)	Total N (%)	p-Value	X^2-Value
Is cervical cancer fundamentally caused by the human papillomavirus (hpv)?					
Yes	242 (61.4%)	152 (38.6%)	394 (100%)	0.000	31.009
No	22 (27.5%)	58 (72.5%)	80 (100%)		
Is infection with the human papillomavirus a prevalent sexually transmitted infection?					
Yes	199 (58.2%)	143 (41.8%)	342 (100%	0.079	3.088
No	65 (49.2%)	67 (50.8%)	132 (100%)		
Do you know about the various HPV strains?					
Yes	76 (45.8%)	90 (54.2%)	166 (100%)	0.001	10.174
No	188 (61%)	120 (39%)	308 (100%)		
Are you aware that early diagnosis of precancerous lesions can be aided by cervical screening?					
Yes	176 (59.1%)	122 (40.9%)	298 (100%)	0.055	3.681
No	88 (50%)	88 (50%)	176 (100%)		
Can cervical cancer prevention and therapy benefit from early diagnosis of precancerous lesions?					
Yes	204 (58.6%)	144 (41.4%)	348 (100%)	0.033	4.538
No	60 (47.6%)	66 (52.4%)	126 (100%)		
Does cervical cancer take a long time to develop from precancerous lesions?					
Yes	166 (54.6%)	138 (45.4%)	304 (100%)	0.523	0.409
No	98 (57.6%)	72 (42.4%)	170 (100%)		
Do you know that Getting Vaccinated Against HPV can stop Cervical Cancer from developing?					
Yes	135 (54.4%)	113 (45.6%)	248 (100%)	0.563	0.335
No	129 (57.1%)	97 (42.9%)	226 (100%)		
Your resource for HPV screening information is?					
Books	30 (50%)	30 (50%)	60 (100%)	0.037	10.196
Social Media	78 (48.8%)	82 (51.2%)	160 (100%)		
Healthcare Workers	86 (60.6%)	56 (39.4%)	142 (100%)		
Friends	35 (55.6%)	28 (44.4%)	63 (100%)		
Newspaper/ Magazines	35 (71.4%)	14 (28.6%)	49 (100%)		
What are the Cervical Cancer risk factors?					
More than one sexual partner	170 (64.2%)	95 (35.8%)	265 (100%)	0.000	54.662
HPV	153 (61.9%)	94 (38.1%)	247 (100%)		
Early sexual activity onset age	71 (52.6%)	64 (47.4%)	135 (100%)		
Increasing Parity	37 (52.1%)	34 (47.9%)	71 (100%)		
Prolonged use of hormonal contraceptives	73 (53.7%)	63 (46.3%)	136 (100%)		
Current or previous sexually transmitted infections	127 (64.8%)	69 (35.2%)	196 (100%)		
Smoking	97 (70.8%)	40 (29.2%)	137 (100%)		

The mean knowledge score was recorded to be 9.68 ± 2.457. Out of 474 participants, 232 (48.9%) had inadequate knowledge about cervical cancer screening, whereas 242 (51.1%) had adequate knowledge about cervical cancer screening. The results also shows that there was significant statistical different found among different age groups and study programs. The findings werew summarized in table 3.

Table 3: Relationship of Adequacy of Knowledge with Demographic Characteristics of Population (Multivariate Analysis)

Variables	Categories	Inadequate Knowledge N (%)	Adequate Knowledge N (%)	Total N (%)	p-Value
Age	17 – 20 Years	76 (45%)	93 (55%)	169 (100%)	0.006
	21 – 23 Years	136 (55.3%)	110 (44.7%)	246 (100%)	
	24 – 27 Years	20 (33.9%)	39 (66.1%)	59 (100%)	
Study Program	Medical	108 (40.9%)	156 (59.1%)	264 (100%)	0.000
	Non-Medical	124 (59%)	86 (41%)	210 (100%)	
Year of study	Junior Year	128 (47.9%)	139 (52.1%)	267 (100%)	0.619
	Senior Year	104 (50.2%)	103 (49.8%)	207 (100%)	
Marital Status	Single	213 (48%)	231 (52%)	444 (100%)	0.103
	Married	19 (63.3%)	11 (36.7%)	30 (100%)	
Total	-	232 (48.9%)	242 (51.1%)	-	-

Presents the participants' attitudes toward cervical screening. A significant majority (80.4%) believed that young women should undergo early screening for HPV (p-Value = 0.000), while 80.6% recommended HPV vaccination for women (p-Value = 0.031) as shown in table 4.

Table 4: Attitude of the Participants towards Cervical Cancer Screening

Variables	Medical N (%)	Non-Medical N (%)	Total N (%)	p-Value	X^2-Value
Should young women get HPV screenings done earlier, in your opinion?					
Yes	228 (59.8%)	153 (40.2%)	381 (100%)	0.000	13.529
No	36 (38.7%)	57 (61.3%)	93 (100%)		
Would you suggest routine screening to identify precancerous lesions early on?					
Yes	190 (55.7%)	151 (44.3%)	341 (100%)	0.988	0.000
No	74 (55.6%)	59 (44.4%)	133 (100%)		
Do you believe that HPV vaccinations for young women are necessary?					
Yes	222 (58.1%)	160 (41.9%)	382 (100%)	0.031	4.667
No	42 (45.7%)	50 (54.3%)	92 (100%)		

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In terms of young women's practices related to cervical cancer prevention, 14.1% of the participants reported smoking (p-Value = 0.000), 18.6% had undergone a pap smear previously (p-Value = 0.032), and 17.9% had received the HPV vaccine (p-Value = 0.077). The findings were mentioned in table 5.

Table 5: Practices of the Participants towards Cervical Cancer Prevention

Variables	Medical N (%)	Non-Medical N (%)	Total N (%)	p-Value	X^2-Value
Are you a smoker?					
Yes	24 (35.8%)	43 (64.2%)	67 (100%)	0.000	12.492
No	240 (59%)	167 (41%)	407 (100%)		
Have you had a pap test done previously?					
Yes	40 (45.5%)	48 (54.5%)	88 (100%)	0.032	4.594
No	224 (58%)	162 (42%)	386 (100%)		
Do you have an HPV vaccination?					
Yes	40 (47.1%)	45 (52.9%)	85 (100%)	0.077	3.131
No	224 (57.6%)	165 (42.4%)	389 (100%)		

DISCUSSION

Particularly affecting women in prospering and developing nations, cervical cancer is still a major global health concern. With a high morbidity and mortality rate, cervical cancer continues to be a threat to women's health despite advances in medical technology and expanded awareness efforts. With that in mind, the purpose of this study was to assess the knowledge, attitudes, and practices around cervical cancer screening among both medical and non-medical female students in our locality. According to a study by Gismondi M *et al.*, only 28.8% of participants recognized HPV as the risk factor for cervical cancer and that same study reported that 23.5% knew that having multiple sexual partners was another risk factor, which in our study was reported to be known by 55.9% of the participants [13]. However, our study showed that a good percentage (83.1%) of the participants of human papillomavirus as the cause of cervical cancer. Comparably, 72% of participants in a study by Singh J mentioned having several sexual partners as a risk factor for cervical cancer [14]. Taking into account the methods for preventing cervical screening while we reported 17.9% of individuals were vaccinated against HPV, Patel IS *et al.*, stated that just 8% of their subjects had received the vaccination [15]. Padmanabha N *et al.*, stated that 18% of their participants had never heard of vaccine against HPV and 21% were vaccinated [16]. Likewise, only 14.8% of respondents in a different study by Tadesse A reported having good understanding about cervical cancer screening, which is less than with our findings showing 51.1% of respondents had adequate knowledge [17]. We discovered that 14.1% of participants had smoked before and 28.9% of participants acknowledged smoking as a risk factor. Gebregziabher D *et al.*, also showed that 7% of individuals indicated quitting smoking as a preventive measure against cervical cancer [18]. The low level of knowledge and practice among the study participants was also mentioned in another study conducted in Ethiopia by Endalew DA *et al* [19]. In the current study, 28.7% of participants acknowledged using contraceptive pills as a risk factor, whereas 46% of individuals in a study by Altamimi T [20]. In contrast to the 18.4% of our participants who had had a pap smear, 47% of respondents nationwide in a study by Hirani S *et al.*, showed that they had heard about pap smears before, of which 73% had had one [10]. In contrast, a negative attitude regarding HPV vaccination and Pap smear screening was noted in a different study conducted in Karachi, Pakistan by Riaz L *et al* [21]. Despite potential biases such as cross-sectional study design, voluntary participation, and limited generalizability, the study's strengths include its well-defined objectives, statistically determined representative sample size, comprehensive statistical analysis using SPSS, and a structured questionnaire evaluating participants' knowledge of cervical screening prevention.

CONCLUSIONS

The medical students were more knowledgeable about cervical cancer screening as compared to the non-medical. It seemed that about half of the participants had adequate knowledge of cervical cancer screening. It was also concluded that even though the participants didn't participate in many preventive measures, most participants had positive attitudes towards early diagnosis, screening and HPV vaccination. Future research should focus on specified areas according to the findings of this study. These shall include the design and evaluation of intervention aimed at improving knowledge, attitude, and practices towards the screening, studying barriers to participation, which include logistical, cultural belief systems, and fear. In this respect, looking toward healthcare providers, cost-effectiveness of screening programs and psychosocial factors regarding attitude and perception is important.

Authors Contribution

Conceptualization: KK, SZ[1], FU, SZ[2]
Methodology: KK, SZ[1], FU, SZ[2], NS, U,
Formal analysis: KK, SZ[1], NS, U, USUR, HG, SM, JS
Writing, review and editing: KK, SZ[1], USUR, HG, SM, JS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

The Diagnostic Accuracy of Conventional Breast Ultrasound in Diagnosing Malignant Breast Lesions Taking Histopathology as Gold Standard

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ABSTRACT

Breast cancer is a prominent worldwide health issue, with difficulties in detection worsened by the presence of dense breast tissue. Ultrasound and other alternative diagnostic methods have demonstrated potential to enhance detection rates, especially in situations involving thick breast tissue. **Objective:** To evaluate how well conventional breast ultrasonography can accurately differentiate between benign and malignant tumors, using histopathology as the most reliable method of comparison. **Methods:** A cross-sectional study was conducted at a tertiary care hospital to evaluate 185 female patients with breast lesions using sonographic examination. Demographic information, ultrasonography results and histopathological data were gathered and examined using SPSS version 26.0. Calculations were performed to determine the sensitivity, specificity, positive predictive value, negative predictive value and diagnostic accuracy. **Results:** The study demonstrated that conventional breast ultrasound has a high diagnostic accuracy rate, with ratings of 91.07%, 83.57%, 89.47%, 85.92%, and 88.11% for sensitivity, specificity, positive predictive value and negative predictive value, respectively. Statistically significant differences in diagnostic accuracy were observed when stratification was performed based on age, duration of disease, parity, and history of breastfeeding. **Conclusions:** The findings indicated that ultrasound is highly effective in differentiating between benign and malignant breast lesions, with substantial diagnostic precision. However, false positives remain a concern, necessitating ongoing research for optimizing ultrasound efficacy, especially in high-risk cohorts.

INTRODUCTION

Breast cancer is one of the most prevalent malignancies worldwide and it contributes to a significant number of cancer related mortalities and morbidities. With an estimated 2.3 million new cases globally, the disease is still a major public health issue that needs to be managed [1]. One notable challenge in breast cancer diagnosis is the presence of dense breast tissue, complicating the detection of abnormalities through standard mammography and increasing the risk of undetected malignancies [2]. This limitation underscores the need for alternative diagnostic modalities, such as ultrasound, which has demonstrated potential in improving detection rates, particularly in cases of dense breast tissue [3]. Ultrasound guided core biopsy offers a less invasive and more convenient alternative to surgical biopsy for evaluating suspicious breast lesions, significantly reducing patient discomfort and healthcare costs [4, 5]. However, the high incidence of benign findings in pathologic reports highlights the importance of accurate differentiation between benign and malignant lesions [6]. Imaging features observed on ultrasound have shown promise in distinguishing between these lesion types, potentially reducing the need for invasive diagnostic procedures [7]. Histopathology remains the gold standard

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for confirming breast cancer diagnoses, but its invasive nature, costliness, and patient reluctance underscore the importance of exploring non-invasive alternatives [8]. The Breast Imaging Reporting and Data System (BI-RADS) is a standardized format and terminology that "The American College of Radiology" has implemented. This system is essential for the production of imaging reports. Traditional B-mode ultrasonography examines breast lesions and the tissues around them by measuring a number of parameters. The Breast Imaging Recording and Data System (BIRADS) categorizes these ultrasonic characteristics according on their size, shape, margin, border, posterior acoustic features, echo pattern and calcification. Benign tumors have BIRADS values of 2 or 3, whereas malignant ones have scores of 4 or 5. Nevertheless, BIRADS classification is still up in the air when there is a lot of overlap in the ultrasonography characteristics of a lesion [9]. In our local context, literature is scarce on the accuracy of mammography and ultrasonography in distinguishing between malignant and benign breast masses, particularly in the context of BI-RADS classification, which categorizes findings on a scale from grade zero to grade six, with higher numbers indicating a higher likelihood of malignancy [10]. Consequently, the objective of our investigation was to evaluate the precision of sonography and mammography features, as well as their "BI-RADS" grades, in the diagnosis of breast malignancies in accordance with pathology findings. Although ultrasound has the capacity to accurately diagnose breast lesions, the reported sensitivity and specificity values exhibit substantial variation among studies. Consequently, the objective of this investigation is to evaluate the diagnostic proficiency of conventional breast ultrasound in the differentiation of benign and malignant lesions, employing histopathology as the gold standard.

This research aimed to improve clinical practice, reduce the need for superfluous interventions and alleviate patient burden by providing local evidence on the reliability of ultrasounds.

METHODS

The study recruited female patients presenting with breast lesions for sonographic evaluation at the Department of Radiology, Combined Military Hospital, Sialkot. Patients underwent conventional breast ultrasound, with subsequent biopsy for histopathological confirmation. From December 2022 to May 2023, a descriptive, cross-sectional study was implemented to prospectively gather relevant data. With a 25% breast cancer prevalence and a 95% confidence interval, an online sample calculator was used to establish that 185 individuals would be the appropriate sample size [11]. Consecutive sampling was employed to collect data for the study. Inclusion criteria encompassed female patients aged 25-75 years with palpable breast masses undergoing biopsy. Exclusion criteria included patients undergoing chemotherapy, those with breast implants and those unable to provide informed consent. Demographic and clinical data were collected and patients underwent conventional breast ultrasound. The "Toshiba Xario 200 US machine" was used to do conventional US and characteristics, with probe frequencies ranging from "7.5 to 13 MHz". The lesion's size and other features were investigated by running the analysis in B-mode in every conceivable plane. Bi-RADS scores were recorded and patients were categorized as positive or negative based on operational definitions. Biopsy was performed by a consultant surgeon, with histopathology reports verified by pathologists. The research and ethics committee of AFPGMI reviewed and approved the study proposal (RE: 344-AAA-ERC-AFPGMI) on August 16, 2022. Informed consent was obtained from all participants and data confidentiality was ensured throughout the study. The data analysis was conducted using SPSS version 26.0. Quantitative data were presented as mean and standard deviation, while qualitative variables were reported as frequency and percentage. Sensitivity, specificity, positive predictive value, negative predictive value, and diagnostic accuracy of ultrasonography were assessed using 2x2 tables. The data were categorized by age, parity, duration of symptoms, and history of nursing, followed by the calculation of "sensitivity, specificity and diagnostic accuracy".

RESULTS

The study included a total of 185 participants, with 97 (52.43%) falling in the age range of 25-50 years and 88 (47.57%) in the 51-75 years age group. Regarding the duration of disease, 112 (60.54%) participants had been experiencing symptoms for six months or less, while 73 (39.46%) had symptoms for more than six months. In terms of parity, 20 (10.81%) participants were primiparous and 165 (89.19%) were multiparous. Additionally, 134 (72.43%) participants had a history of breast feeding, while 51 (27.57%) did not as shown in table 1.

Table 1: Demographic Characteristics of the Study Sample

Variables	Number of Patients N (%)
Age (Years)	
25-50	97 (52.43)
51-75	88 (47.57)
Duration of Disease	
≤ 6 Months	112 (60.54)
>6 Months	73 (39.46)
Parity	
Primiparous	20 (10.81)
Multiparous	165 (89.19)
History of Breastfeeding	
Yes	134 (72.43)
No	51 (27.57)

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The diagnostic accuracy of conventional ultrasonography in distinguishing between benign and malignant breast lesions was assessed. Among the patients with positive results on histopathology, ultrasound detected True Positive (TP) cases in 102 instances, indicating accurate identification of malignant lesions. However, there were also 12 False Positive (FP) results, where ultrasound incorrectly identified benign lesions as malignant. Conversely, among patients with negative results on histopathology, ultrasound correctly identified True Negative (TN) cases in 61 instances, indicating accurate identification of benign lesions. However, there were 10 False Negative (FN) results, where ultrasound failed to identify malignant lesions. The p-value of 0.0001 indicates a statistically significant difference in the diagnostic accuracy of conventional breast ultrasound. Using histology as the gold standard, conventional breast ultrasonography had a sensitivity of 91.07%, specificity of 83.57%, positive predictive value of 89.47%, and negative predictive value of 85.92% and diagnostic accuracy of 88.11% when it came to differentiating benign from malignant breast lesions as shown in table 2.

Table 2: The Accuracy of Conventional Breast Ultrasonography in Distinguishing between Benign and Malignant Breast Lesions, with Histology Serving as the Reference Standard

Ultrasonography	Histopathology		p-Value
	Positive	Negative	
Positive	102 (TP)	12 (FP)	0.0001
Negative	10 (FN)	61 (TN)	

"TP=True positive; FP=False positive; FN=False negative; TN=True negative"

Significant insights were obtained with statistically significant p-values ($p < 0.001$) from the stratification of diagnostic accuracy according to age groups, length of illness, parity and history of nursing. With a sample size of 97 individuals ranging from 25 to 50 years old, ultrasonography demonstrated a sensitivity of 92.73%, specificity of 78.57%, PPV of 85.0%, NPV of 89.19%, and diagnostic accuracy of 86.60%. In contrast, the diagnostic accuracy was 89.77%, sensitivity was 90.47%, specificity was 90.32%, PPV was 94.44% and NPV was 82.35% in the group of people aged 51-75 (n=88). The ultrasonography had a sensitivity of 92.19%, specificity of 79.17%, PPV of 85.51%, NPV of 88.37% and diagnostic accuracy of 86.61% about the length of the disease, for cases with a duration of 6 months or less (n=112). With a sensitivity of 91.0%, specificity of 84.62%, PPV of 90.09%, NPV of 85.94% and diagnostic accuracy of 88.48% among 165 multiparous women, the results were favorable. A sensitivity of 93.55%, specificity of 90.0%, PPV of 93.55%, NPV of 90.0%, and diagnostic accuracy of 92.16% were recorded for non-breastfeeding women (n=51), while a sensitivity of 82.76%, specificity of 87.95%, PPV of 85.71%, and diagnostic accuracy of 87.05% were recorded for breastfeeding women (n=134) as shown in table 3.

Table 3: Stratification of Diagnostic Accuracy Concerning Demographic Variables

Variables	Ultrasonography	Histopathology		p-Value
		Positive	Negative	
Age				
25-50 Years (n=97)	Positive	51 (TP)	09 (FP)	0.001*
	Negative	04 (FN)	33 (TN)	
51-75 Years (n=88)	Positive	51 (TP)	03 (FP)	0.001*
	Negative	06 (FN)	28 (TN)	
Duration of Disease				
≤ 6 Months (n=112)	Positive	59 (TP)	10 (FP)	0.001*
	Negative	05 (FN)	38 (TN)	
> 6 Months (n=73)	Positive	38 (TP)	9 (FP)	0.001*
	Negative	6 (FN)	20 (TN)	
Parity				
Primiparous (n=20)	Positive	11 (TP)	02 (FP)	0.001*
	Negative	01 (FN)	06 (TN)	
Multiparous (n=165)	Positive	91 (TP)	10 (FP)	0.001*
	Negative	09 (FN)	55 (TN)	
H/O Breastfeeding				
Yes (n=134)	Positive	73 (TP)	10 (FP)	0.001*
	Negative	08 (FN)	48 (TN)	
No (n=51)	Positive	29 (TP)	02 (FP)	
	Negative	02 (FN)	18 (TN)	

*= P<0.05

The ROC curve (the blue line) was closer to the top-left corner, indicating ultrasound as strong classifier. Following an appropriate range of cutoff values, a successful diagnostic test should have a minimal false positive and false negative rate, as seen in the graph. Ultrasonography had high classification performance, with an AUC-ROC value of 0.85 as shown in figure 1.

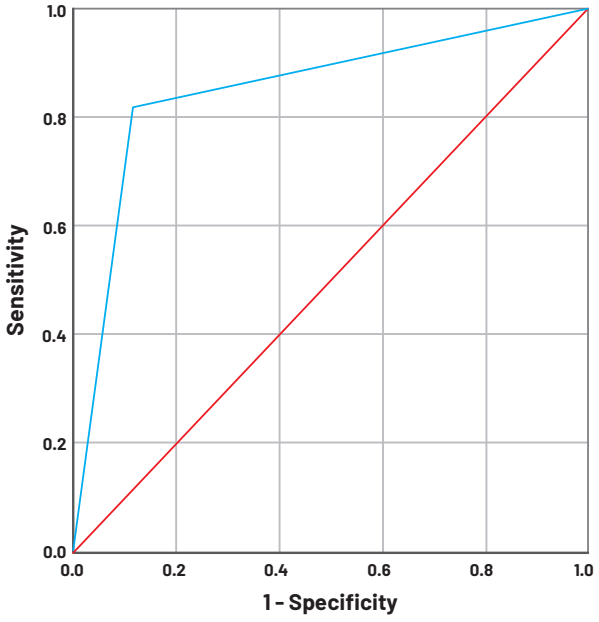

Figure 1: ROC Curve for Breast Ultrasonography

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DISCUSSION

Numerous non-invasive and sonographically-based approaches are the subject of active investigation with the goal of decreasing the frequency of invasive biopsies used to diagnose cancerous breast lesions. In recent years, ultrasonography has assumed a more crucial role in the detection of breast cancer. Ultrasound of the breast is the technique of choice when a patient is experiencing symptoms during a clinical assessment. When performed on asymptomatic individuals, breast ultrasonography is thought to offer a greater sensitivity for detecting breast cancer in high-risk women, those younger than 50 and those with dense breast tissue. If a breast mammogram only revealed part of a lump or nodule, if there is the mammographic asymmetry in the area of a palpable lesion, if there are breast implants, if there has been a lumpectomy or segmentectomy or if there is no abnormality detected on mammography, then a breast Ultrasound-Guided Biopsy (USG) may be necessary. In 10–40% of cases, ultrasound may discover tumors that are not visible on mammography; the incidence of detection varies with patient age and breast density [12, 13]. Our study found that conventional breast ultrasound had "diagnostic accuracy, specificity, sensitivity and positive and negative predictive values" of 88.11%, 83.57%, 89.47%, 85.92%, and 81.07% in distinguishing benign from malignant breast lesions, respectively, when compared to histopathology, the gold standard. These results are consistent with previous studies. Ultrasonography had a sensitivity of 72.6% and a specificity of 88.5%, according to a study that compared USG with mammography [14]. Additional research has shown that breast ultrasonography is 86.8% sensitive and 72.4% specific in terms of distinguishing benign breast lesions from malignant [11]. According to the research done by Guyer PB and Dewbury KC the specificity was 97.2% and the sensitivity was 91.2%. [15]. A local study in Pakistan found that ultrasonography has a "sensitivity and specificity" of 95.24% in detecting breast cancer and a "specificity" of 68.75% [16]. According to another research by Akhtar MS *et al.*, USG has a specificity of 70.0%, sensitivity of 77.8%, and accuracy of 75.7% when it comes to diagnosing malignant tumors [17]. It may be noted that the significance of ultrasonography in the context of breast cancer evaluations has heightened, which is evident from studies pointing to increased reliance on this diagnostic method in pragmatic clinics. Similar findings were found in our study that around 61% of patients were found to have malignant breast lesions from ultrasound, indicating the diagnostic value of the technique. The malignance of the lesion was further substantiated by the histopathological examination, which reported the condition in 60.86% of the patients. The results mean that the method is legitimate in the identification of lesions, which can be considered suspicious based on the ultrasound results. Interestingly, more than 90% of the patients that found coverage in the positive group had true malignant breast lesions, and still, the need for histopathology results is necessary to clarify the presence of false positives in this group. In this vein, false positives are represented in the form of two patients set against a total of 21 positive patients. In this sense, two out of 21 cases in the positive ultrasound group were false positives. It may be noted that the interpretation of ultrasound findings needs to be looked at cautiously and needs to be validated by histopathology. In the case of the negative group, the histopathology results showed that 16 patients included in the group were diagnosed with malignant breast lesions. In this vein, in 25% of the cases within this group, there has been a risk of false negatives. However, the majority of the cases falling in this specific group were true negatives 75%. It, therefore, means that the method was able to identify the benign lesions appropriately in the negative group. It may be worth mentioning here that situations, where breast ultrasound may be necessary, include studies indicating a palpable mass not satisfying the limitations of mammography, studies showing cysts to be distinguished from solid nodules and palpable abnormalities corresponding to mammographic asymmetry [16]. Importantly, ultrasound can detect mammographically occult cancers in a significant percentage of cases, highlighting its potential as a diagnostic tool in cancer detection [18]. Literature has shown that the most accurate way to diagnose breast disorders, including cancer, is by using a mix of imaging techniques and histological examination. Magnetic Resonance Imaging (MRI) has been demonstrated to be very sensitive and accurate in diagnosing breast cancer, however, mammography and ultrasound are also vital in this process [17-19]. Furthermore, prior research has shown that advanced ultrasonography methods, such as Doppler, might be used to selectively image breast tumors [20, 21]. Histopathology is the gold standard for confirmation, but a combination of digital mammography and ultrasound greatly improves sensitivity, diagnostic accuracy, and negative predictive value in detecting malignant breast neoplasms [22]. Sometimes a breast ultrasound may be a helpful diagnostic tool, especially in situations when a biopsy is not required. There is also the possibility that ultrasound screening may provide findings that are falsely positive. Therefore, in the future, research should be conducted to determine whether or not ultrasonography is beneficial in detecting breast cancer in those who are at high risk for developing the disease. One radiologist was responsible for carrying out all of the ultrasonography in this study. This was done in an attempt to eliminate any possibility of bias that could have been present. It is possible to test it with a large number of operators in order to guarantee that it is accurate in terms of diagnosis and to achieve inter-observer reliability. This is because the procedure is dependent on talent. The current study is the first of its kind in the local community and it

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demonstrates the potential of ultrasonography in the diagnosis of breast tumors that are cancerous. The findings of this study suggest that ultrasound need to be the first method of investigation for female patients who present with breast lumps; if the ultrasonography reveals the presence of cancer, a biopsy ought to be carried out. The use of this technology has the potential to significantly reduce the number of biopsies that are carried out on benign breast tumors.

CONCLUSIONS

The research findings indicated that ultrasonography showed high levels of specificity, sensitivity and negative and positive predictive values in distinguishing between benign and malignant breast masses. Diagnostic ultrasonography is a highly efficient method for differentiating between benign and malignant breast abnormalities.

Authors Contribution

Conceptualization: SQA
Methodology: SB, SG, SK
Formal analysis: SQA
Writing, review and editing: HM, HS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

Effect of Smoking on Retinal Nerve Fiber Layer Alterations and Dry Eye Disease in Chronic Smokers

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ABSTRACT

Smoking has an impact on the eyes as well because the toxins it contains cause blood flow to be reduced and obstructions to develop in the ocular capillaries, depriving the eye of nutrients that are crucial to its health. **Objectives:** To evaluate impact of smoking on thickness of the Retinal Nerve Fiber Layer(RNFL)and symptoms of dry eye in chronic smokers. **Methods:** This study was conducted at Madinah Teaching Hospital, Faisalabad in duration of Sep-Dec, 2023. 30 smokers (60 eyes) who had smoked ≥ 25 cigarettes a day for 10 years were enrolled. For comparison, an equal number of healthy non-smoker were participated as controls. Using a self-structured proforma, data were collected using a non-probability purposive sampling technique. In addition to a thorough history evaluation, a comprehensive slit-lamp examination was performed. schirmer test, Tear Film Breakup Time (TBUT), meibomian gland dysfunction grading and Optical Coherence Tomography (OCT) for RNFL examination were performed. SPSS software was used for analyzing the data. **Results:** Average age was 49 ± 1.78 years. Each participant was male. Mean schirmer value for smokers was 8 ± 1.71, while the average for non-smokers was 17 ± 1.36 (p=0.02). Similarly, smokers had a tear breakup time of 6 ± 1.89, while non-smokers had a tear breakup time of 15 ± 1.27(p=0.00). According to the results, smokers' tear film stability is considerably less than that of non-smokers. RNFL thinning was detected in all quadrants in smokers compared to non-smokers (p=0.00). **Conclusions:** Smoking over an extended period of time is associated with a higher risk of developing dry eye disease and thinning of RNFL.

INTRODUCTION

Tobacco smoking is the most preventable cause of morbidity in the world, taking the lives of seven million individuals each year [1]. Smoking has a negative effect on eye health as well. The carcinogens in tobacco reduce blood flow and cause blockages to form in the capillaries of the eyes, which results in a shortage of essential nutrients required to maintain the eyes healthy [2]. Smokers have larger concentrations of activated platelets, leukocytes and erythrocytes than non-smokers possess. This results in increased blood viscosity and a higher risk of thrombus formation in blood vessels [3, 4]. When these factors combine together, it elevates the risk of ocular ischemia, interference with cellular functions, and eventually contribute to a variety of ocular conditions [5]. The complex condition referred to as Dry Eye Disease (DED) is represented by anomalies in the tear film along with symptoms such as inflammation, redness, sensitivity to light and blurred vision [6]. Numerous factors, including medication, age, gender, lifestyle choices and systemic diseases, can influence the development of Dry Eye Disease (DED)[7, 8]. Untreated cases of severe dry eye may end to blindness, infectious keratitis, and corneal scarring [9]. Since smoking can lead to peroxidation of the pre-corneal tear film, the outermost layer of the tear film, it has

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been determined that smoking constitutes a major risk [10, 11]. Through the metabolic and vascular effects of systemically absorbed products, cigarette smoking causes damage that has been shown to be a risk factor for atherosclerotic problems in the cerebral, aortic and coronary circulations [12, 13]. Free radicals are created by oxidizing substances found in tobacco smoke, which have the ability to cause cell damage and death. Smoking has dose-dependent hazards for the eyes, with an increase in smoking index being correlated with an increase in morbidity [14]. Smokers who already have visual disorders such as diabetic retinopathy or glaucoma may experience faster optic nerve degeneration since these ailments already impair the Retinal Nerve Fiber Layer (RNFL). Thickness of retinal nerve fiber layer varies in smokers [15]. This study was carried out in order to fill a specific research gap, even though a substantial amount of literature already suggests that smokers are more likely to develop dry eye disease and that there is not much knowledge on the effects on the Retinal Nerve Fiber Layer (RNFL). The current study examines the thickness of the Retinal Nerve Fiber Layer (RNFL) and symptoms of dry eye in long term smokers.

METHODS

A pilot study was conducted at Madinah Teaching Hospital, Faisalabad in duration of September 2023 to December 2023. Participants in the study were thirty smokers (sixty eyes) who regularly smoked at least twenty-five cigarettes per day for 10 years. A letter of ethical approval for this research (TUF/IRB/248) was issued by the University of Faisalabad, Ethical Institutional Review Board on August 11, 2023. Based on a review of the literature and an empirical approach, the sample size has been found as 30 participants. A consequence of the study's time constraints was the small sample size. Participants in the study included 15 smokers (30 eyes) and 15 healthy people (30 eyes), matched for age and sex. For comparison, an equal number of healthy non-smokers with no other systemic or ocular disease were participated as controls. As a recruited thirty smokers (60 eyes) who smoked at least twenty-five cigarettes a day. Individuals who smoked 25 cigarettes or more a day for 10 years were considered habitual chronic smokers. Nonprobability purposive sampling technique was used to collect the data. Participants in the study ranged in age from 35 to 45 years, having clear media, an intraocular pressure below 20 mmHg, a spherical refraction between +2.0 and -2.0 diopters, and Best Corrected Visual Acuity (BCVA) of 20/20 or better. Those with a history of ocular surface conditions that impair tear production or secretion such as sjogren's syndrome, Stevens-johnson's syndrome, allergic or infectious conjunctivitis, blepharitis, long-term contact lens wear, notable lid abnormalities or dry eye disease were excluded. Individuals who had undergone recent eye surgery within the previous three months, a history of ocular trauma or chemical burns, frequent use of visual display systems, glaucoma, retinal disorders, optic nerve pathology or other underlying problems were also eliminated. Following the guidelines set forth in the Declaration of Helsinki, prior approval was sought from the institutional ethical committee and consent was given by each participant. Demographic data were obtained, such as the patients' ages, gender. The inclusion criteria for this study were limited to people who had smoked 25 cigarettes a day for ten years. The number of cigarettes smoked regularly was one of the beneficial indicators of smoking duration. A comprehensive slit-lamp examination was performed to examine the anterior and posterior segments, in addition to a detailed investigation of the patient's history. Every patient was subjected to the Schirmer's I test, Tear Film Breakup Time (TBUT), and Optical Coherence Tomography (OCT) for Retinal Nerve Fiber Layer (RNFL) assessment. Tear breakup time and the anterior segment were examined under a slit-lamp biomicroscope. Prior the exam, the severity of the dry eye was assessed using the OSDI questionnaire. The patients' symptomatology was evaluated using the Ocular Disease Surface Index (OSDI) questionnaire, which has a scale from 0 to 100. Higher scores are indicative of greater severity of symptoms. This assessment was then split up into four groups for categorization considerations. People who scored in the range of 0 to 12 were categorized as having normal indications. Individuals with scores ranging from 13 to 22 were classified as having mild dry eyes, while those with scores between 23 and 32 were classified as having moderate dry eyes. People who scored 33 or higher were classified as having extremely dry eyes. This classification made it possible to get a thorough grasp of the different levels of symptom severity among the individuals. An extensive evaluation of the ocular surface was performed. The Tear Film Breakup Time (TBUT) and Schirmer's I test were performed. The thickness of the RNFL was assessed by optical coherence tomography. Each of the RNFL's four quadrants the nasal, superior, inferior, and temporal was evaluated separately. Statistical Package for Social Sciences (SPSS version 22.0) was used for analyzing the data. The age distribution and OSDI grading in both groups were evaluated using descriptive statistics. Variables including the Schirmer test, TBUT, and retinal nerve fiber layer thickness were compared between smokers and non-smokers in all quadrants using an independent t-test.

RESULTS

The participants' average age was 49 ± 1.78 years. Each participant was male. A descriptive statistical analysis included frequency distributions of the Ocular Surface Disease Index (OSDI) grading for both groups: smokers and non-smokers. Higher scores on the Ocular Disease Surface

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Index (OSDI) questionnaire reflect more severe symptoms. The scale rages from 0 to 100. Nineteen individuals in the nonsmoker group of this study were defined as having a normal state without dry eyes, while 6 individuals were diagnosed as having mild dry eye using the OSDI scale. Three of the smoker group's members were found to have mild dry eye symptoms, while eight were found to have moderate symptoms. In addition, four subjects showed signs of severe dry eye as in shown in table 1.

Table 1: Ocular Disease Surface Index (OSDI)

OSDI	Grading	Smokers N (%)	Non-Smokers N (%)
0 to 12	Normal	-	9 (60%)
13 to 22	Mild Dry Eyes	3 (20%)	6 (40%)
23 to 32	Moderate Dry Eyes	8 (53.33%)	-
33 and above	Severe Dry Eyes	4 (26.66%)	-

An independent t-test was conducted to statistically analyze dry eye parameters - Schirmer test I (mm) and TBUT (sec) of both groups: smokers and non-smokers. The mean Schirmer value for smokers was 8 ± 1.71, while the average for non-smokers was 17 ± 1.36 (p=0.02). Similarly, smokers had a tear breakdown time of 6 ± 1.89, while non-smokers had a tear breakup time of 15 ± 1.27 (p=0.00). According to these results, smokers' tear film stability is considerably less than that of non-smokers as in shown in table 2.

Table 2: Tear Film Assessment

Variables	Smokers (Mean ± SD)	Non-Smokers (Mean ± SD)	p-Value
TBUT (sec)	6 ± 1.8	15 ± 1.27	0.00
Schirmer test I (mm)	98 ± 1.71	17 ± 1.36	0.02

An independent t-test was conducted to figure out the thickness of the nerve fiber layer in all quadrants for both groups: smokers and non-smokers. RNFL thinning was detected in all quadrants specifically superior and inferior quadrants in smokers compared to non-smokers (p=0.00). This study reveals that subjects with a positive history of smoking had a lower retinal nerve fiber layer (RNFL) as compare to nonsmokers as shown in table 3.

Table 3: Thickness of Nerve Fiber Layer in Smokers and Non-Smokers (n=15)

Retinal Nerve Fiber Layer Thickness (µm)	Smokers (Mean ± SD)	Non-Smokers (Mean ± SD)	p-Value
Superior	109 ± 8.31	116 ± 9.03	0.00
Inferior	111 ± 11.4	121 ± 13.31	0.00
Temporal	65 ± 9.34	73 ± 11	0.04
Nasal	72 ± 13.71	81 ± 10.5	0.02

DISCUSSION

Smoking produces a variety of deleterious changes to the human body, including variations to the eyes, which increase the risk of disease and early mortality [16]. Smoking alters the lipid layer of the tear film, decreases basal secretion, decreases corneal and conjunctival sensitivity, lowers tear lysozyme concentration and can accelerate the onset of squamous metaplasia in the conjunctiva, among other changes to the ocular surface [17, 18]. A popular approach for measuring basal and reflex tear secretion is the Schirmer test. Smoking is known to cause lipid peroxidation, which damages the pre-corneal tear film. The Schirmer test results for smokers and nonsmokers were measured and compared in this study. The findings showed that smokers' levels were much lower than those of nonsmokers [19, 20]. Schirmer's test readings have also been found to be lower in smokers in previous studies, with one study finding that the reduction persisted as pack-years increased [21]. Smoking cigarettes causes histological alterations in the conjunctiva as well as alters the tear film's protein composition. Conjunctival and corneal sensitivity are reduced as a consequence of these modifications to the subbasal corneal nerve plexus. Schirmer measurements and basal tear secretion consequently drop. The inflammatory mediators from smoking, which can cause long-term inflammation of the ocular surface, are another potential reason. Further lowering reflex secretion could result from neurosecretory blockage brought on by this medical condition [22]. In a comparable way, research discovered that smokers' TBUT values were much lower than those of nonsmokers. Similar results were observed in the studies by Satici A *et al.*, and Khalil HE *et al.*, which showed that smokers' TBUT was considerably lower than that of nonsmokers' [21, 23]. The main explanation appears to be a biochemical assault by the free radicals in cigarette smoke on the lipid layer of the pre-corneal tear film. Damage is also exacerbated by cellular and inflammatory processes on the surface of the eyes. There is a clear correlation between smoking and reduced tear film quantity and quality. In this study, the thickness of the RNFL was evaluated in smokers and nonsmokers. Additionally, RNFL in each quadrant was assessed and the results indicated a significant decline in each quadrant favoring the adverse effects of smoking on the retina. This study is in line with a study by Dervişoğulları MS *et al.*, who discovered the similar effects of smoking on RNFL in their investigation and recommended taking this into account when interpreting the results in those who smoke [24]. Another study carried out in Turkey corroborated Demirci S *et al.*, suggestion that smoking causes a decrease in RNFL [25]. In their study, Nita M *et al.*, also mentioned that smoking may result in a number of ocular pathologies [26]. Individuals who have smoked heavily over an extended period of time in past times show a decrease in the thickness of the Retinal Nerve Fiber Layer (RNFL). Rather than the duration of smoking, the quantity of smoking seems to be more directly linked to this reduction. This reduction could be due to nicotine's direct neurotoxic effect on the optic nerve as well as its vasoconstrictive effects, which reduce blood flow [27]. This study concluded that subjects with a positive history of smoking had a lower Retinal Nerve Fiber Layer (RNFL). This study's

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strength, focuses exclusively on the consequences of heavy smoking over an extended period of time on the health of the eyes, particularly the integrity of the Retinal Nerve Fiber Layer (RNFL) and the incidence of dry eye. This comprehensive approach highlights how smoking significantly affects the quantity and quality of tear films, highlighting the need for vision specialists to inform smokers about these potential risks. In future, including RNFL thickness measures into early detection techniques may improve the capacity to effectively prevent and manage smoking-related ocular disorders. This study promotes proactive health education among smokers to protect their overall health and vision..

CONCLUSIONS

In conclusion, the study's results show that smoking has a negative impact on the overall health of the ocular surface, with the consequences becoming more noticeable with increased smoking frequency. Smoking specifically aggravates dry eye and thinning of the retinal nerve fiber layer.

Authors Contribution

Conceptualization: MJ
Methodology: MJ, MIK, AB, MAC
Formal analysis: MAV, MAC
Writing, review and editing: KMI, FR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Cutaneous Tuberculosis: A Clinicopathological Study in A Tertiary Care Hospital

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ABSTRACT

Tuberculosis (TB) is a chronic disease that can affect multiple organs including, the skin. Cutaneous TB poses a great challenge to dermatologists due to its varied clinical presentations and non-specific histopathological findings. **Objective:** To determine the frequency of clinicopathological patterns of Cutaneous Tuberculosis in children and adults in a Tertiary Care Hospital. **Methods:** A descriptive cross-sectional study included 63 patients diagnosed with Cutaneous TB at the Department of Dermatology, Dr. Ruth KM Pfau Civil Hospital, Karachi, Pakistan from January 2020 to December 2022. All the patients were clinically evaluated and histopathological features were recorded. **Results:** The common age group was 21-30 years, with male predominance. Lupus Vulgaris was the most common clinicopathological type in 46 cases (73%), followed by Scrofuloderma in 9 cases (14.3%). Tuberculous Verrucosa cutis and Tuberculous Gumma accounted for 4.8% of cases, while Acute Military Tuberculosis and Tuberculous Panniculitis accounted for 1.6% of cases. The most predominant morphology of the lesion was Erythematous Plaque (36.5%) and the most commonly affected site was face (30.2%). Epitheloid Granuloma with langerhans giant cells were typically present in most of the cases, with Caseous Necrosis more predominantly seen in Scrofuloderma (44.4%), TB Gumma (66.6%) and Acute Military TB (100%). **Conclusions:** Lupus Vulgaris is the most common presentation of Cutaneous TB followed by Scrofuloderma. Epitheloid Granuloma with langerhans giant cells, with or without Caseous Necrosis is the predominant histopathological presentation. Clinical and histopathological assessment is crucial for an appropriate diagnosis.

INTRODUCTION

Tuberculosis stands the second most common cause of death from infectious diseases, leading to death of nearly 2 million people annually [1]. Every year approximately 8 million new T.B cases are reported, with 80% affecting young and middle-age adults. This not only impacts the productive economies of nations but also significantly influences the quality of life for individuals [1, 2]. In 2020, thirty countries accounted for about 86% of the new T.B cases. Amongst these, eight countries reported the highest number of cases. India tops the list followed by Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh and South Africa. Collectively, these countries contribute to half of the global disease burden and exhibit highest morbidity and mortality rates [3]. Extrapulmonary Tuberculosis (EPTB) is one of the major causes of morbidity and mortalility in both under-developed and emerging nations, comprising about 20-30% of all active TB cases [4, 5]. It can occur in organ systems other than the lungs and spreads hematogenously. Cutaneous TB constitutes 1.5% of all cases of Extrapulmonary Tuberculosis caused by Mycobacterium Tuberculosis but Mycobacterium Bovis and rarely bacilli Calmette-Guerin (BCG) are sometimes involved [6]. This disease exhibits varied clinical presentations influenced by factors such as the route of infection (endogenous or exogenous) and cellular immune status of the host. Cutaneous lesions manifest in various forms, including papules, plaques, nodules, ulcers, hypertrophic and verrucous lesions [7]. According to the recent classification, TB has been categorized into paucibacillary forms (few mycobacteria, difficult to isolate, like Lupus Vulgaris, Tuberculosis Verrucosa Cutis) and multibacillary forms (numerous mycobacteria, like

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Scrofuloderma, Tuberculous Chancre, Acute Miliary Tuberculosis) [8]. The diagnosis of cutaneous TB is established based on clinical features and confirmed through histopathology and culture with or without molecular testing. A comprehensive assessment of systemic involvement is essential in every instance [9].

The objective of the study was to identify the different clinical patterns of cutaneous TB that are histopathologically confirmed in skin biopsy specimens.

METHODS

A descriptive cross sectional study, that included 63 patients of Cutaneous Tuberculosis. This study was conducted at the Department of Dermatology, Dr. Ruth KM Pfau Civil Hospital, Karachi, Pakistan from January 2020 to December 2022. The study included patients newly diagnosed with Cutaneous Tuberculosis, irrespective of gender and age. While patients with incomplete or missing clinical or pathological data related to Cutaneous TB, or who had a previous diagnosis/treatment for Cutaneous TB were excluded from the study. The sample size was calculated by taking estimated frequency of Tuberculosis Gumma 8.23% and desired margin of error 7% [10]. Permission from the ethical committee of our institute, Dow University of Health Sciences (IRB-3435/DUHS/EXEMPTION/2024/96, Dated; 28 March 2024) was taken and consent was obtained from all patients included in the study. All the patients underwent a detailed clinical history, local lesion assessment, physical and systemic assessments, and a series of diagnostic tests including hematological tests, chest X-ray, sputum culture (for those exhibiting positive chest symptoms). Additionally, Mantoux test and HIV testing by ELISA method were performed. Biopsies were conducted in all clinically suspected cases, with formalin-fixed tissues were processed and stained with hematoxylin and eosin stain, as well as Ziehl-Neelsen stain. Determination of clinicopathological type of Cutaneous TB was the main study objective. Data were analyzed using SPSS version 23.0.

RESULTS

Total 63 cases of Cutaneous TB were clinically diagnosed and subsequently confirmed through histopathology. Of these cases, 32 (50.8%) were male and 31 (49.2%) were female, out of which 11 (17.4%) were children. The age range was 6-70 years, with the most predominant age group being 21-30 years in 31.7% of cases. Upon evaluating the patient's history, family history was present in 9 (14.3%) cases, trauma history in 16 (25.4%) cases, fever was documented in 9 (14.3%) cases, weight loss in 6 (9.5%) cases, and lymphadenopathy in 16 (25.4%) cases. Additionally, 5 (7.9%) patients had a history of Pulmonary Tuberculosis, and Pott's Disease was present in only 1 (1.6%) patient (Table 1).

Table 1: Age-Wise Distribution of Cases (n=63)

Age Group (Years)	Frequency (%)
0-10	7 (11.1%)
11-20	15 (23.8%)
21-30	20 (31.7%)
31-40	7 (11.1%)
41-50	6 (9.5%)
51-60	5 (7.9%)
61-70	3 (4.8%)

The majority of patients presented with a single lesion, observed in 35 (55.6%) cases. In the overall cases, 23 cases (36.5%) had erythematous plaques, 19 cases (30.2%) had ulcerated plaques and 7 cases (11.1%) had draining sinuses. Hyperkeratotic plaques were seen in 6 cases (9.5%), nodules in 4 (6.3%) cases, and abscesses in 4 cases (6.3%). The most common site involved was the face (30.2%) followed by the foot (25.4%). The most common site involved was the face (30.2%) followed by the foot (25.4%). Less common sites included the forearm/arm and neck (11.1% each), as well as the gluteal/perineal region and abdomen (4.8% each). Knee injuries represented (3.2%), while the axilla was the least common site at (1.6%). (Figure 1).

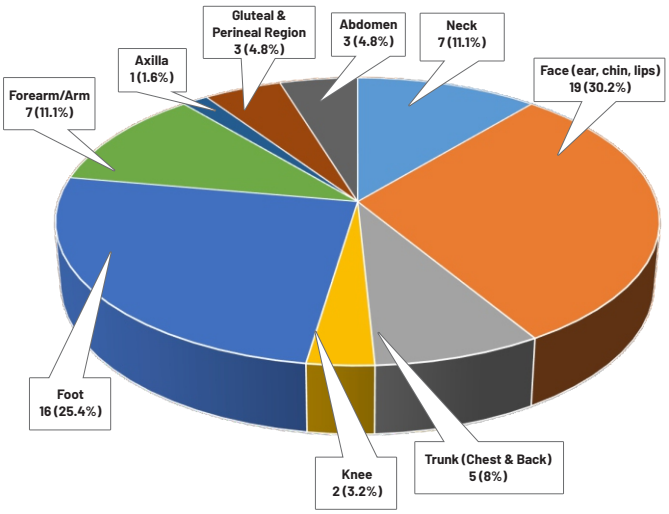

Figure 1: Site of Involvement in Cutaneous Tuberculosis. (n=63)

Lupus Vulgaris was the most common type of Cutaneous TB, observed in 46 patients (73%), and followed by Scrofuloderma in 9 cases (14.3%). Tuberculous Verrucosa Cutis and Tuberculous Gumma were each observed in 3 cases (4.8%), while Acute Military Tuberculosis and Tuberculous Panniculitis were diagnosed in 1 case (1.6%) each. Out of 11 cases of Cutaneous TB in children, 8 cases (72.7%) were Lupus Vulgaris, 2 cases (18.2%) were of Scrofuloderma, and 1 case (9.1%) of Tuberculous Verrucosa Cutis (Figure 2).

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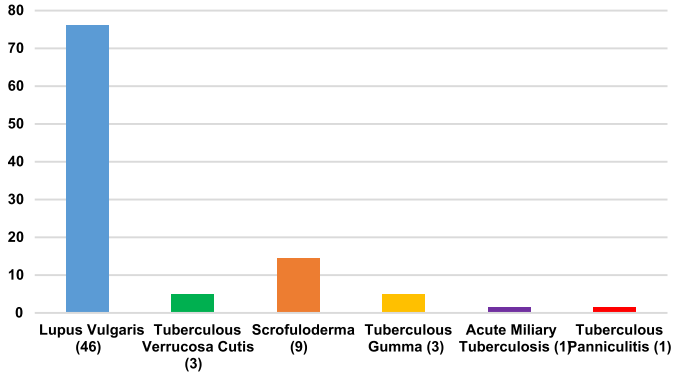

Figure 2: Distribution of Different Clinicopathological Subtypes of Cutaneous Tuberculosis. (n=63)

Lupus Vulgaris was the most common variant of our study followed by Scrofuloderma. Other less common variants were Tuberculous Verrucosa Cutis (TVC), Tuberculous Gumma, Acute Miliary Tuberculosis, and Tuberculous Panniculitis. In Lupus Vulgaris, the face (19/46, 41.3%) was the most commonly involved site, while in Scrofuloderma, the neck (6/9, 66.6%) was the predominant site. Among the three cases of Tuberculous Verrucosa cutis, the most frequently observed site was the foot (2/3, 66.6%). On histopathology, all 63 cases (100%) showed epitheloid granulomas surrounded by lymphocytes. Out of these cases, 38 patients (60.3%) exhibited well-formed epitheloid granuloma, whereas 25 patients (39.7%) demonstrated ill-defined epitheloid granuloma. Langerhans giant cells were observed in 52 cases (82.5%), while chronic inflammatory cells in 11 cases (17.5%). Caseous necrosis was absent in 36 cases (78.2%) of Lupus Vulgaris. However, it was present in 18 (28.6%) cases out of the total, which included 10 (21.8%) cases of Lupus Vulgaris, 4 (44.4%) cases of Scrofuloderma, 2 (66.6%) cases of Tuberculous Gumma, 1 case (33.3%) of Tuberculous Verrucosa cutis, and in all cases (100%) of Acute Military Tuberculosis (Table 2).

Table 2: Distribution of Demographic, Clinical, and Histopathological Findings According to the Cutaneous Tuberculosis Clinicopathological Subtypes

Features	Lupus Vulgaris n (%)	Scrofuloderma n (%)	Tuberculous Verrucosa Cutis n (%)	TB Gumma n (%)	Acute Miliary TB n (%)	TB Panniculitis n (%)
Number of Cases	46 (73%)	9 (14.3%)	3 (4.8%)	3 (4.8%)	1 (1.6%)	1 (1.6%)
Male	26	3	2	1	-	-
Female	20	-	7	2	1	1
Most Common Lesion Observed	Erythematous plaque	Draining sinus	Hyperkeratotic plaque	Nodule	Ulcerated plaque	Draining sinus
Most Common Site Involved	Face 41.3%	Neck 66.6%	Foot 66.6%	-	-	-
Epidermis						
Intact	27 (58.7%)	4 (44.4%)	-	-	1 (100%)	1 (100%)
Focal Ulceration	8 (17.4%)	4 (44.4%)	-	-	-	-
Pseudoepitheliomatos Hyperplasia	10 (21.7%)	1 (11.1%)	3 (100%)	3 (100%)	-	-
Atrophy	1 (2.2%)	-	-	-	-	-
Dermis						
Granuloma Type	Well-formed 58.7%	Well-formed 66.6%	Well-formed 6.6%	Well-formed 66.6%	Well-formed 100%	Ill-defined 100%
Langerhans Giant Cells	37 (80.4%)	8 (88.8%)	3 (100%)	3 (100%)	-	1 (100%)
Chronic Inflammatory Infiltrate	9 (19.6%)	1 (11%)	-	-	1 (100%)	-
Caseation Necrosis	10 (21.8%)	4 (44.4%)	1 (33.3%)	2 (66.6%)	1 (100%)	Absent

DISCUSSION

Cutaneous TB is prevalent in Pakistan, but the exact incidence and prevalence remain unknown due to the paucity of literature. However, an older study from Pakistan demonstrated a frequency of 3.69% for cutaneous tuberculosis, as diagnosed by skin biopsies [11]. In our study, 31.7% of patients fell within the second and third decades of life, with a male predominance, aligning with findings in existing literature [12]. Skin trauma due to increased physical activity during younger age and early exposure to active TB cases may underlie this age-related predilection. In our study, the face was the most commonly affected site (30.2%), followed by the foot. Interestingly, these results contrast with studies from India and Indonesia, where the lower limb was frequently involved [13-15]. However, some literature reports indicate the head, neck, and face as common sites [16, 17]. This disparity may stem from variations in the prevalence of different clinical variants of cutaneous TB across diverse regions. In our study, LV emerged as the predominant clinical type in both children and adults, accounting for 73% of the cases, consistent with findings in existing literature [18-20]. Notably, Hammami *et al.*, and Maghwal et al., had previously reported scrofuloderma as the most common type; however, in our observations, it constituted the second most frequent clinical type at 14.3% [12, 21]. In cases of LV among our patients, it typically manifests as an erythematous plaque on the face. Conversely, patients with scrofuloderma exhibited discharging sinuses on the

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neck. Diagnosing cutaneous TB is intricate and demands a high index of suspicion. Several concurrent laboratory investigations are often required, encompassing culture, histology, demonstration of acid-fast bacilli (AFB) on stains, a positive tuberculin skin test (TST), evidence of systemic TB, and response to treatment. While a positive culture provides a definite diagnosis, its sensitivity is low due to a paucity of mycobacteria in skin lesions. Furthermore, nonspecific histology presents an additional challenge in rendering a diagnosis [9]. Nonetheless, it remains crucial to employ histopathologic assessment, mycobacterial stains, and culture from skin biopsy samples for the accurate diagnosis of cutaneous TB. The classical histopathological presentation in the current study comprised epitheloid granuloma with Langerhans giant cells. Noteworthy variations in histopathological features were observed among different clinical variants, including the presence or absence of caseous necrosis and the formation of well-formed (tuberculoid) or poorly formed granulomas. In our study, 18 (28.6%) cases exhibited caseous necrosis, with the highest percentages found in scrofuloderma (44.4%), TB gumma (66.6%) and acute military TB (100%). This picture represents low host immunity, particularly in the context of these multibacillary TB types.

CONCLUSIONS

In current study, Lupus vulgaris constituted the majority of cutaneous TB cases, with the face being the most frequent location. The majority of patient fell within 21-30 year age group, with male predominance. Establishing a proper diagnosis necessitates a clinic-histopathological assessment. It is important to examine for concurrent tuberculous infections in other organs since cutaneous TB may be associated. There is an urgent need for additional multi-centered studies to gather comprehensive clinical, epidemiological and histopathological data on cutaneous tuberculosis in Pakistan.

Authors Contribution

Conceptualization: HU, NR
Methodology: HU, NR
Formal analysis: HU, NR, WS, BUR, RM
Writing-review and editing: HU, NR, WS, BUR, RM, ZS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Evaluating the Efficacy of Combined Surgery for Cataract and Glaucoma: A Comparative Analysis of Visual Acuity, Intraocular Pressure, and Anterior Chamber Depth

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ABSTRACT

Glaucoma is characterized by an abnormal increase in intraocular pressure, leading to optic nerve damage and permanent visual impairment. Cataract is characterized by lens opacity that impairs vision but can be reversed. **Objective:** To compare pre and post-operative average visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth in patients with cataract and narrow angle glaucoma undergoing combined phacoemulsification, intraocular lens implantation, and trabeculectomy. **Methods:** A quasi-experimental study was carried out at Niazi Welfare Foundation Teaching Hospital Sargodha from June 2022 to December 2023. Total 107 patients with both cataracts and narrow angle glaucoma were included. Post-surgery, average visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth were assessed at various postoperative intervals (1 day, 1 week, 1 month, 3 months, and 6 months). The Patient's symptoms improved, with visual acuity and average anterior chamber depth increasing by more than 50% compared to pre-surgery was considered as significant. Data were analyzed by SPSS version 25.0. P-value <0.05 was considered as significant. **Results:** Results of the study yielded significant improvements in average visual acuity, intraocular pressure (IOP), anterior chamber angle, and anterior chamber depth post-operatively with complication rate of 6.52%. **Conclusions:** We concluded that combined phacoemulsification with intraocular lens implantation (IOL) and trabeculectomy may be an effective approach for managing intraocular pressure (IOP) and improving visual acuity in patients with narrow angle glaucoma and cataract.

INTRODUCTION

Glaucoma is characterized by an abnormal increase in intraocular pressure, leading to optic nerve damage and permanent visual impairment whereas cataracts result from lens opacity that impairs vision [1, 2]. The vision loss from glaucoma is irreversible, while cataract-induced vision loss can be reversed [3]. Cataracts are the leading cause of blindness globally, affecting around 15.2 million people and accounting for approximately 51% of blindness cases. Glaucoma is the third most common cause of visual impairment worldwide, impacting about 3.6 million individuals [4]. In Asia, the incidence of these diseases is notably high. The region accounts for over half of the global burden of cataracts, largely due to a higher prevalence of risk factors such as UV exposure, malnutrition, and limited access to healthcare. Glaucoma prevalence in Asia is also significant, with primary angle-closure glaucoma being particularly common [5]. In Pakistan, cataracts are the primary cause of blindness, responsible for about 60-80%

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of all blindness cases [6]. Glaucoma is a major public health concern, with many undiagnosed and untreated cases leading to severe vision loss. Cataract and glaucoma are the two main causes of blindness in Pakistan, contributing to 12.2% and 7.1% of cases, respectively. It is estimated that a considerable proportion of patients undergoing cataract surgery also have concurrent glaucoma [7]. Cataracts primarily manifest as blurred vision and progressive visual decline [2]. After the onset of the disease, the patient's lens increases in volume during the expansion period, causing the iris septum to move forward [8]. The increase in intraocular pressure may even induce glaucoma. Senile cataracts typically occur due to age-related lens degeneration [9]. In the early stages, mild lens opacity has a minimal effect on vision, but as it advances, vision deteriorates and can lead to blindness [10]. In patients with both cataract and glaucoma, the consequences are often severe and complex leading to exacerbated visual impairment, greatly reducing the patient's quality of life [11]. Cataract cause clouding of the eye's lens, leading to blurred vision, glare, color distortion, and difficulties in daily activities like reading and driving [12]. At the same time, glaucoma progressively damages the optic nerve, causing peripheral vision loss, tunnel vision, and potentially complete blindness if left untreated [13]. Current treatment for cataract involves phacoemulsification with intraocular lens implantation, which is widely regarded as the gold standard [14]. For glaucoma, the management includes medications, laser therapy, and surgical interventions like trabeculectomy [15]. However, these treatments have their shortcomings. Cataract surgery alone does not address the elevated intraocular pressure (IOP) in glaucoma patients, and glaucoma surgeries like trabeculectomy can be associated with complications and variable success rates [16]. Phacoemulsification cataract extraction can crush the hardened lens nucleus into a chyle through the front ultrasonic needle, and the emulsified lens tissue is sucked out by the perfusion suction system, which does not affect the constant fluid flow in the eye. This treatment method has the advantages of minimal trauma, mild postoperative reaction, and promotes the patient's vision to recover as soon as possible after surgery [17]. However, phacoemulsification cataract extraction cannot effectively solve iris bulging and angle adhesion. Combined with trabeculectomy surgery, the sinus trabecular tissue and surrounding iris tissue can be directly removed after the lens is implanted [18]. The combination of phacoemulsification, intraocular lens implantation, and trabeculectomy in a single procedure is a newer approach aimed at addressing both cataract and glaucoma simultaneously. This combined surgery has several benefits, including a single recovery period, reduced overall risk of complications compared to separate surgeries, and improved patient compliance. Additionally, it offers the potential for better visual outcomes and more effective IOP control, making it a promising alternative to the current standard of care [17].

Therefore, understanding these effects is crucial to evaluate the impact of surgical interventions on visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth. By investigating these parameters, we aim to provide insights into the comprehensive benefits of the combined surgical approach in managing cataract and angle closure glaucoma for optimizing treatment strategies and improving clinical outcomes.

METHODS

Quasi experimental study was conducted from June 2022 to December 2023 at Niazi Welfare Foundation Teaching Hospital Sargodha, involving 107 patients with both cataracts and narrow angle glaucoma. The sample size was calculated based on the assumption that the decrease in IOP (outcome variable) pre- and postoperatively by using the mean differences in intra-ocular pressure (1.311+ 2.97 mmHg) at an alpha level of 0.05 and power of 90% [19]. Non-probability convenient sampling method was used. The study received IRB approval (NM&DC/IRB/128 on dated 1st June, 2022) and informed consent was obtained from all participants. Inclusion criteria for the study were: a) Patients on gonioscopy showing a Schaffer grading of 2 or less in at least two quadrants for narrow angle glaucoma; b) Patients with nuclear sclerosis grade-I, cortical, posterior subcapsular & mixed cataract; c) Patients who had undergone conservative treatment for angle closure glaucoma with two or more drugs before surgery, without improvement in IOP, anterior chamber depth; d) patients having IOP> 21mmHg; e) Patients having increased cup-to-disc ratio (≥0.6) with corresponding visual field defects; f) Presence of lens opacification affecting vision, assessed using the Lens Opacities Classification System III (LOCS III) at slit lamp. An exclusion criterion was: a) Retinal detachment; b) Advanced corneal disease; c) Patients with severe visual impairment (e.g. worse than 20/200) primarily due to other ocular conditions; d) Patients with NPL; e) Severe liver and kidney diseases to minimize perioperative risks & ensure proper postoperative recovery; f) Previous ocular surgeries; g) Mental illness. The demographic characteristics of the participants were documented. Prior to the procedure, clinical data such as treatment regimen, average visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth were also recorded. Patients underwent phacoemulsification cataract extraction, intraocular lens implantation, and trabeculectomy. Post-surgery, average visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth were assessed at various postoperative intervals (1 day, 1 week, 1 month, 3 months,

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and 6 months). 1 month post-operative findings were compared with pre-operative to assess the study outcome. The outcomes were categorized as follows: 1) Effective: Patient's symptoms improved, with visual acuity and average anterior chamber depth increasing by more than 50% compared to pre-surgery; 2) Ineffective: Patient's symptoms showed no significant improvement, and visual acuity did not recover. Statistical analysis was conducted using SPSS 24.0 software. Treatment indicators, including visual acuity and intraocular pressure, were represented as ($\bar{x}$ + s), and paired t-test was utilized to compare treatment effects pre- and post-surgery. A significance level of $p < 0.05$ was considered statistically significant.

RESULTS

The study involved 107 patients, comprising 62 males (58%) and 45 females (42%), aged between 56 and 87 years, with an average age of (71.52±5.76) years. The duration of the disease ranged from 3 to 6 years, with an average of (3.15±1.22) years are shown in Table 1.

Table 1: Demographic Characteristic

Characteristics	N (%)
Male	62(58)
Female	45(42)
Age (Y)	56 - 87
Mean Age (Y)	71.52 ± 5.76
Disease Duration (Y)	3 - 6
Mean Duration (Y)	3.15 ± 1.22

The analysis of ophthalmic parameters revealed a notable difference in average visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth. These parameters showed significant improvement compared to their pre-treatment values ($p < 0.05$), as shown in Table 2.

Table 2: Comparison of Ophthalmic Parameters ($\bar{x} \pm s$)

Parameter	Preoperative	After Surgery	p-value
Average visual acuity	0.32 ± 0.11	1.12 ± 0.21*	0.00
Mean Intraocular Pressure Measurement (mmHg)	43.52 ± 4.35	9.25 ± 1.48*	0.00
Average Anterior Chamber Angle	171.52 ± 32.52	61.52 ± 3.52*	0.00
Average Anterior Chamber Depth (mm)	1.82 ± 0.23	3.15 ± 0.31*	0.00

Note: Significant (*) compared to the pre-treatment group, $p < 0.05$.

The primary complications included inflammation in the anterior chamber, corneal edema, iris injury, among others, with a total incidence of 6.98% illustrated in table 3.

Table 3: Post-operative Complication Rate N (%)

Number of Cases	Anterior Chamber Inflammation	Corneal Edema	Iris Injury	Overall Incidence
107	3 (2.8)	2 (1.86)	2 (1.86)	7 (6.52)

DISCUSSION

Cataract and glaucoma are prevalent eye diseases. Cataracts typically result from metabolic imbalances in the lens, leading to protein denaturation and cloudiness. Symptoms include blurred vision, sensitivity to light, and dimmer vision [3]. Glaucoma is characterized by a sustained increase in intraocular pressure, which can harm various eye tissues and visual function. Severe damage to the optic nerve can result in permanent, irreversible blindness. Hence, prompt and effective treatment is crucial for improving the prognosis of patients with these conditions [9]. Currently, surgery stands out as the most effective treatment for patients dealing with both cataracts and narrow angle glaucoma [17]. However, numerous studies indicate that managing only glaucoma in such cases could exacerbate cataract formation, while solely addressing cataracts may not resolve the damage inflicted by narrow angles glaucoma, leaving the risk of blindness unmitigated. This underscores the challenge of achieving optimal treatment outcomes with a single approach [15]. In this study, phacoemulsification cataract extraction, intraocular lens implantation and trabeculectomy were performed on patients with cataract and narrow angle glaucoma. The results showed that post-surgery, there was a significant improvement in average visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth ($p< 0.05$). This treatment approach appears to be more effective for patients, enhancing their vision significantly. A study conducted by Wang B *et al.*, about the effects of combining phacoemulsification and intraocular lens implantation with trabeculectomy. The results demonstrated that the overall effective rate in the observation group was significantly higher compared to the control group ($P < 0.05$). Additionally, in another research, patients in the observation group showed greater improvements in both vision and anterior chamber depth than those in the control group, highlighting the effectiveness of the combined surgical approach in enhancing ophthalmic outcomes [18]. Other research studies also provide comprehensive data regarding the effects of phacoemulsification, intraocular lens (IOL) implantation, and trabeculectomy on various ophthalmic parameters. These studies consistently depict significant improvements in visual acuity post-operatively, highlighting the effectiveness of these combined surgical procedures in enhancing patient outcomes [20]. The post-surgery complication rate was minimal at 6.52%. Other Research studies also indicate a lower incidence of complications following phacoemulsification cataract aspiration, intraocular lens implantation combined with trabeculectomy [21]. This study provides a comprehensive approach for patients with both cataract and narrow angle glaucoma, addressing multiple aspects of ophthalmic parameter such as visual acuity, intraocular pressure, anterior chamber angle, and anterior chamber depth. By using a quasi-experimental design, the study can provide

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valuable insights into real-world outcomes, ensuring the results are applicable to clinical practice. However, the study also has some limitations. Despite these limitations, the study's comprehensive assessment of combined surgical interventions in a specific patient population provides valuable data that can inform future clinical practices and research.

CONCLUSIONS

Phacoemulsification cataract extraction, intraocular lens implantation and trabeculectomy on patients with cataract and narrow angle glaucoma is of paramount significance as it remarkably improves the patients' visual acuity along with other ophthalmic parameters.

Authors Contribution

Conceptualization: MSM
Methodology: MSM
Formal analysis: MZC, SAS, UTM, NS
Writing-review and editing: MA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

Safety of Long Acting Reversible Contraception (LARC) during 3 Months of Follow up at Civil Hospital, Karachi

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ABSTRACT

Contraception counseling is an essential component of family planning services. It provides the foundation for delivering correct information on contraceptive methods and eliminating myths regarding risks and negative effects. **Objectives:** To determine the Safety of Long-Acting Reversible Contraception (LARC) for postpartum contraception during 3 months of follow-up. **Methods:** A cross sectional descriptive study comprised on total of 108 women aged 25-35 years who accepted LARC in the postpartum period at Department of Obstetrics and Gynaecology, Civil Hospital, Karachi from 22nd February 2021 to 21st August 2021, were included. Females with uterine abnormalities and severe anemia were excluded. The demographic information (name, age, registration number) was taken. The women were counseled regarding postpartum contraception LARC such as IUD or Jedelle (implant) during the antenatal period and LARC was placed within 30 minutes of placental delivery. Those women who selected LARC were called for follow-up for 3 months in OPD and at follow-up visits, patients were assessed for their safety of this method. **Results:** The age range in this study was from 25 to 35 years with a mean age of 28.81 ± 3.27 years. The majority of the patients 80 (74.07%) were between 25 to 30 years of age. The mean parity was 3.10 ± 0.72. In this study, the safety of Long Acting Reversible Contraception (LARC) for postpartum contraception during 3 months of follow-up was found in 91 (84.26%) women. **Conclusions:** This study concluded that long acting reversible contraceptives in the immediate postpartum period are very safe.

INTRODUCTION

According to the 2023 Census (as per WHO), Pakistan ranks fifth in the world with a population of 245 million people [1]. This necessitates action to stabilize Pakistan's population. Pakistan is still lagging behind in terms of contraceptive use and family size limits. Pregnancies that are spaced too closely offer health concerns to both mothers and babies. Poorly spaced pregnancies have been linked to poor mother and child health outcomes across the globe. Pakistan has a high fertility rate of 3.8 children per woman and a low contraceptive prevalence rate of 35% [2, 3]. The unmet demand for contraception is around 65%. Lack of understanding, a lack of accessible family planning clinics and cultural and socioeconomic issues that restrict women's mobility are all causes of poor contraceptive usage [4]. If the birth takes place in a hospital setting, the moment of delivery gives the ideal chance to address their need for contraception [5]. Contraception counseling provides the foundation for delivering correct information on contraceptive methods and eliminating myths regarding risks and negative effects [4]. Furthermore, it offers suitable contraceptive recommendations to meet family planning needs and optimize pregnancy spacing [5]. In a cluster randomized trial carried out in 40 reproductive health clinics across the United States from 2011 to 2013,

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the proportion of women who received contraceptive counseling in the intervention group was higher than the proportion of women who received standard contraceptive care in the control group (2.3% vs. 2.0%) and the pregnancy rate was lower in the intervention group (7.9 vs. 15.4 per 100 person-years) [6]. In one research, 56.9% of patients accepted one of the contraceptive techniques exclusively during their hospital stay. The most popular contraceptive technique was an intrauterine device (45.0%), followed by injectables (15%), tablets (10%), and condoms (8%) [7]. Kumar S *et al.*, revealed that pregnancy of continuation of LARC is 62.8% owing to the lack of any problem [8]. The complication rate of immediate after placental IUCD implantation was 40.4% in prior research. In this investigation, IUCD was shown to be safe in 59.6% of cases [9]. Another research showed that IUCD is safe in 83.57% of cases [10].

The study's goal was to assess the safety of LARC in the local community. There is practically little literature on this issue in Pakistan. International research on this issue is available, although they indicate heterogeneity in LARC safety [9-11]. As a result, this study was designed to determine the Safety of Long-Acting Reversible Contraception (LARC) for postpartum contraception during 3 months of follow-up.

METHODS

In this descriptive study, conducted from February 22, 2021, to August 21, 2021, a sample size of 108 was determined based on a 95% confidence level, 7% margin of error and a prior study's reported safety proportion of 83.57% for Intrauterine Contraceptive Devices (IUCD) [10]. Non-probability consecutive sampling was employed. Inclusion criteria involved women aged 25 to 35 years with willing partners for LARC, while primigravida, those with uterine abnormalities and severe anemia (Hb less than 7.0g/dl) were excluded. After obtaining ethical approval, 108 eligible women from the Gynaecology Department at Civil Hospital, Karachi were enrolled and informed consent was obtained. Demographic information was collected and patients were counseled on LARC options during the antenatal period. LARC placement occurred within 30 minutes of placental delivery and a three-month follow-up in the outpatient department assessed the method's safety, looking for complications such as pain at the implant site, abdominal pain and heavy menstrual bleeding. Data, including age, parity, socio-economic status, education, contraceptive method and complications, were recorded. Statistical analysis was performed using SPSS version 25.0. The data were normally distributed (assessed via Shapiro-Wilks test). Quantitative data were presented as Mean ± S.D. and qualitative variables were presented as frequencies and percentages. Post-stratification chi-square tests were used to account for effect modifiers with a significance level taken at $p \leq 0.05$.

RESULTS

The age of participants varies from 25 to 35 years with a mean age of 28.81 ± 3.27 years. The majority of the patients 80 (74.07%) were between 25 to 30 years of age. The mean parity was 3.10 ± 0.72. The distribution of patients according to socioeconomic status, place of residency occupation, education, and contraceptive as shown in table 1.

Table 1: Descriptive Statistic

Variables	Frequency (%)
Socioeconomic Status	
<20000	10 (9.26%)
20000-50000	41 (37.96%)
>50000	57 (52.78%)
Place of Residency	
Rural	38 (35.19%)
Urban	70 (64.81%)
Occupation	
Non-Working	74 (68.52%)
Working	34 (31.48%)
Education	
Illiterate	19 (17.59%)
Matric	24 (22.22%)
Intermediate	18 (16.67%)
Graduate	47 (43.52%)
Contraceptive Methods	
IUD	73 (67.59%)
Implants	35 (32.41%)
Parity	
Mean Parity	3.10 ± 0.72

In this study, the safety of Long-Acting Reversible Contraception (LARC) for postpartum contraception during 3 months of follow-up was found in 91 (84.26%) women. Out of 17 patients, 11 patients have heavy menstrual bleeding, 05 have abdominal pain and 01 have pain at the implant site, as shown in table 2.

Table 2: Safety of Long Acting Reversible Contraception (LARC) For Postpartum Contraception during 3 Months of Follow-Up

Safety	Frequency (%)
Present	91 (84.26%)
Absent	17 (15.74%)
Complications	
Heavy Menstrual Bleeding	11 (64.71%)
Abdominal Pain	5 (29.41%)
Pain at the Implant Site	1 (5.88%)

Stratification of safety with respect to age, parity, socioeconomic status, place of residency, occupation, education, and contraceptive method are shown in table 3.

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Table 3: Stratification of Safety with Respect to Various Factors

Variables	Safety Frequency (%)		P-Value
	Safe	Not Safe	
Age (Years)			
25-30	67 (83.75%)	13 (16.25%)	0.806
31-35	24 (85.71%)	4 (14.29%)	
Parity			
≤3	61 (80.26%)	15 (19.74%)	0.079
>3	30 (93.75%)	2 (6.25%)	
Socioeconomic Status (SES)			
<20000	8 (80.00%)	2 (20.00%)	0.916
20000-50000	35 (85.37%)	6 (14.63%)	
>50000	48 (84.21%)	9 (15.79%)	
Place Of Residency			
Rural	32 (84.21%)	6 (15.79%)	0.992
Urban	59 (84.29%)	11 (15.71%)	
Occupation			
Non-Working	65 (87.84%)	9 (12.16%)	0.132
Working	26 (76.47%)	8 (23.53%)	
Education			
Illiterate	16 (88.89%)	2 (11.11%)	0.853
Matric	19 (79.17%)	5 (20.83%)	
Intermediate	16 (84.21%)	3 (15.79%)	
Graduate	40 (85.11%)	7 (14.89%)	
Contraceptive Method			
IUD	60 (82.19%)	13 (17.81%)	0.394
Implant	31 (88.57%)	4 (11.43%)	

DISCUSSION

This study reported the use of Long-Acting Reversible Contraception (LARC) for postpartum contraception as highly safe during 3 months of follow-up. Safe and effective contraceptive options, including Intrauterine Devices (IUDs) and contraceptive implants, should be routinely available to nulliparous women and adolescents. In the United States, the Medical Eligibility Criteria (MEC) classify IUD use among nulliparous women and adolescents as Category 2, indicating that the benefits outweigh the risks. Both the American Academy of Pediatrics and the American College of Obstetricians and Gynecologists (ACOG) recommend Long-Acting Reversible Contraception (LARC) methods, such as IUDs, for adolescents [12-14]. Despite the fact that there is no statistically significant difference between the rates of adolescent and adult LARC discontinuation due to depression, national data show that adolescent LARC use is much lower than that of other age groups [15]. The Contraceptive CHOICE study found that 62% of 1,054 young people (age: 14-20 years) who participated were satisfied with and continued using LARC. The percentage of single women who used a LARC increased considerably between 2009 and 2012, from 2.1% to 5.9% [15]. The purpose of this study was to evaluate the security of three months of postpartum contraception with Long-Acting Reversible Contraception (LARC). This study indicated that among the women who used LARC after giving birth, 91 (84.26%) had no adverse reactions. Kumar S. found that 62.8% of pregnancies continued after LARC treatment since there were no complications [8]. Previous studies found a complication risk of 40.4% just after placental IUCD implantation. This study found that IUCD was safe in 59.6% of cases [9]. In another study, IUCD was shown to be risk-free in 83.5% of users. A Cochrane Database Systematic Review on the efficacy and feasibility of IUD insertion after delivery was published in 2010 [16]. This research looked at all randomised controlled trials that used IUD insertions within 10 minutes of placental ejection. It looks safe and effective to implant an IUD just after giving birth, according to the research. However, this research suggested that the rate of expulsion was higher after delivery than it was during interval insertion. Nathalie Kappa *et al.*, also showed that immediate IUD implantation was safe compared to later postpartum time periods and interval insertion in their extensive investigation of intrauterine device insertion during the postpartum period. Expulsion rates were lower for immediate postpartum IUD insertion than for delayed postpartum insertion, but higher than for interval insertion [17]. Immediate IUD insertion after childbirth is standard procedure in countries like India and China. Expulsion rates were lower than expected in two large multicenter research (one including 300 women and the other containing 2,733 women). Infection, perforations, and unexpected pregnancies were just as common in the studies from India and China as they were in the other studies we looked at [18-19]. Expulsion rates more accurately reflected the available literature after a more thorough study with several follow-up evaluations and acknowledgment of persons lost to follow-up [20]. An Indian study found that 23.5% of the 434 women who received a copper IUD had bleeding, 9.0% experienced expulsion and 11.3% experienced trouble seeing the strings [21]. Although not limited to the postpartum period, recent research out of Uganda indicated that women who opted for short-acting techniques over long-acting ones did so because they were concerned about the potential negative effects of LARC [22]. Side effects such as heavy or absent bleeding or the lack of periods have been reported [22]. More than a quarter of more than 1200 Pakistani women who used LARC devices for contraception reported unpleasant symptoms, most often bleeding and pain, according to the study's authors [23]. Thirty percent of patients required further care throughout the 12-month follow-up period due to discomfort caused by side effects [23]. Insertion of an IUD within 10 minutes of placenta birth, early postpartum (10 minutes to 48 hours) and interval/delayed insertion (4-6 weeks postpartum) have all been shown to be safe and effective in four separate clinical investigations. The risk of expulsion was greatest in the first several days following implantation surgery. There was

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no statistically significant difference in the low incidence of infection, uterine perforation, or unwanted pregnancy across the groups [24-27]. Two of the four studies that looked at the three different postpartum insertion timings found a significantly higher expulsion rate in the first few days after delivery and the first few weeks after delivery compared to interval insertion. Results from two randomized controlled trials that looked at just the postpartum and the interval periods [25, 26]. The rate of ejection was higher with vaginal deliveries in all of the included trials [26]. Immediate insertion is safe and effective following either caesarean or vaginal birth, according to the results of six prospective observational studies on IUD implantation during the immediate postpartum period (within 10 minutes post placenta) [27-29]. Menorrhagia was less common in the immediate implantation group because of the varying durations of lactational amenorrhea in the postpartum period. Therefore, overcoming the prejudice of lactational amenorrhea takes more time. One year after having CuT380A implanted within 10 minutes, Khurshid N *et al.*, found that 9 out of every 100 patients had menorrhagia [30]. Spotting was found to be 6% in the post placental group after 1 year of follow-up by Khurshid N *et al.*, in 2000, although studies comparing rapid insertion to extended insertion are few [30]. The effectiveness, safety and subsequent benefits and drawbacks of early post-placental Intrauterine Device (IUD) insertion were studied, including 235 women (74% vaginal births, 26% caesarean sections) [31]. There were checkups at the six-week, six-month, and one-year marks. Continued use was high, with 87.6% and 76.3% at 6 and 12 months following post-placental IUD insertion, respectively. In this study, the Cu-T 380A device had a 12.3% cumulative expulsion rate after 1 year [31].

CONCLUSIONS

This study concluded that long acting reversible contraceptives in the immediate postpartum period are very safe, which can be used in the immediate postpartum period as a reliable and safe method for contraception in order to decrease the complications.

Authors Contribution

Conceptualization: ST
Methodology: ST, AF, MT, SM, DK, SS
Formal analysis: ST
Writing, review and editing: AF, MT, SM, DK, SS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

The Role of Cerebrospinal Fluid High-Sensitivity C–Reactive Protein (CSF hsCRP) in Distinguishing Bacterial Meningitis from Aseptic Meningitis

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ABSTRACT

One of the most prevalent serious diseases in newborns and infants is meningitis. Aseptic meningitis is generally less severe than bacterial meningitis and often has a better prognosis. CRP level is the most useful criterion for diagnosing feverish children with significant infections. **Objective:** The present study aimed to determine the level of CRP in CSF of bacterial meningitis, and aseptic meningitis for early prediction of meningitis and remove the lapse in its treatment. **Methods:** This cross-sectional study was conducted at the Immunology Department of The Children's Hospital & the Institute of Child Health from Jan 2022 to Jan 2023. The present study enrolled patients who had meningitis symptoms (fever, headache, vomiting, and neck stiffness), aged between >2 years to 12 years, both male and female gender. The CRP levels of all patients were measured using the agglutination method. Data were analyzed using IBM-SPSS version 26.0. **Results:** Of the total 45 patients, 20 (44.4%) were males and 25 (55.6%) were females. The mean age of patients was 5.98+2.792 years. From total, 29 (64.4%) had bacterial meningitis while 16 (35.6%) had aseptic meningitis. The 09 (31.03%) bacterial meningitis patients had positive CRP (>3.0mg/L). The present study showed a statistically significant association between CSF-CRP results with bacterial and aseptic meningitis (p=0.003). **Conclusions:** While awaiting the results of other confirmatory tests, CSF-CRP can be utilized as an early diagnostic tool for the identification of bacterial and aseptic meningitis. Additionally, it could aid in the early diagnosis of aseptic vs bacterial meningitis.

INTRODUCTION

The medical disease known as meningitis is defined by the inflammation of membranes that shield the brain and spinal cord. One of the most frequent serious diseases among newborns (less than one month old) and infants (less than one-year-old) is meningitis. The frequency of bacterial meningitis in children varies depending on age group; the highest prevalence is seen in newborns under two months of age [1]. Meningitis is caused by various pathogens, including bacteria, viruses, and fungi. Bacterial meningitis is more severe while viral meningitis is more prevalent [2]. It is common for some bacteria, such as *Neisseria meningitidis*, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Streptococcus agalactiae*, to cause infectious meningitis. Group B *streptococcus* causes bacterial meningitis in newborns. These bacteria also cause other serious illnesses (sepsis and pneumonia) and

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account for almost half of the meningitis deaths that occur worldwide. If untreated, bacterial meningitis is lethal [3]. Between 5 to 20% children and 20 to 50% adults die every year with this condition [4]. Over time, the spectrum of organisms responsible for disease may change. The prognosis for bacterial meningitis has improved because of the availability of novel β-lactam antibiotics, vaccination against *Haemophilus influenzae, pneumococci,* and *meningococci,* better intensive care, and supportive therapy in developed countries [5]. These measures have also decreased the prevalence of bacterial meningitis. The main causes of childhood morbidity and death in developing countries are low vaccination rates, delayed seeking medical assistance, malnutrition, delayed diagnosis, and delayed starting proper antibiotic therapy in cases of bacterial meningitis [6]. Meningitis which is caused by viral infections as opposed to bacteria is known as aseptic meningitis. An inflammation of the meninges that results in pleocytosis of the cerebrospinal fluid, no growth on a standard bacterial culture, and a sudden onset of headache, fever, and stiff neck is known as aseptic meningitis. Common viruses that can cause aseptic meningitis include Enteroviruses, Herpesviruses, and the Mumps virus. Aseptic meningitis is generally less severe than bacterial meningitis and often has a better prognosis, as it tends to resolve on its own with supportive care [7-8]. C-reactive protein (CRP) is an acute-phase inflammatory protein. It has been included in screening tests for febrile children in recent decades [9]. Globally, CRP level is the most useful criterion for diagnosing feverish children with significant infections [10-11]. Due to many reasons, there is a delay in the diagnosis of meningitis patients. Because CSF culture sensitivity takes 48-72 hours for reporting which cause a delay in treatment.

The present study aimed to determine the level of CRP in CSF of bacterial meningitis, and aseptic meningitis for early prediction of meningitis and remove the lapse in its treatment.

METHODS

The present cross-sectional study was conducted at the Immunology Department of The Children's Hospital & the Institute of Child Health from January 2022 to January 2023, after getting ethical approval letter (Ref No.1459/SAHS dated 06 Dec 2021). The sample size of 45 children was calculated by taking positive bacterial meningitis children as 89%, taking 5% margin of error and 95% confidence interval [12]. The present study enrolled the patients who had meningitis symptoms (fever, headache, vomiting, and neck stiffness), aged between >2 years and up to 12 years, both male and female [13]. Patients of more than 12 years of age, and who had other types of brain infections (encephalitis/ brain tumors) were excluded. The lumbar puncture (LP) of suspected patients was performed by a neuro-physician. The CSF samples were received at the pathology laboratory for analysis. The physical examination, gram stain, protein, glucose, and cell count (total and differential leukocyte) were performed. Meningitis was classified as bacterial meningitis based on CSF examination results (increased protein >100 mg/dL, decreased glucose <40 mg/dL, and leukocyte count 100-5000/mm3 with polymorph nuclear leukocyte domination >80%), gram staining results, and/or positive bacterial culture. Conversely, viral meningitis was described as occurring when the bacterial culture was negative but the viral culture, serological tests, pleocytosis, or reverse transcriptase polymerase chain reactions were positive [14]. After the initial arrangements for diagnosis and treatment, and with informed consent about 05cc of blood was taken from each patient and transferred to the Pathology Laboratory. The samples were centrifuged at the speed of 3000 rpm for serum separation. Using the Dot Diagnostic Gmbh Germany Kit (Reference No. ASO/200607, Lot No. 200607), the CRP level of each patient was determined. The normal value of CRP was considered as <3.0mg/L. Data were analyzed using Statistical Package for the Social Sciences version 26.0 (IBM SPSS version 26.0). The quantitative variables were summarized as mean + standard deviation while the qualitative variables were expressed as frequency and percentages. A chi-square test/Fishers exact test was performed to evaluate the association between variables.

RESULTS

In table 1, out of the total 45 patients, 20 (44.4%) were males and 25 (55.6%) were females. The patients had the ages between 02 years to 12 years old. The mean age of patients was 5.98+2.792 years. According to the CSF examination results, the patients were classified into bacterial meningitis and aseptic meningitis. From total, 29 (64.4%) patients had bacterial meningitis while 16 (35.6%) had aseptic meningitis.

Table 1: Demographic and Clinical Characteristics of Study Patients

Characteristics	Frequency (%)
Mean age (Y)	5.98+2.792
Age groups	
02 - 06 (Y)	27 (60.0%)
07 - 12 (Y)	18 (40.0%)
Gender	
Male	20 (44.4%)
Female	25 (55.6%)
Types of meningitis	
Bacterial meningitis	29 (64.4%)
Aseptic meningitis	16 (35.6%)

In figure1, out of a total of 29 bacterial meningitis patients, 13 (44.82%) were males and 16 (55.17%) were females, while from 16 aseptic meningitis patients, 07 (43.75%) were males and 09 (56.25%) were females.

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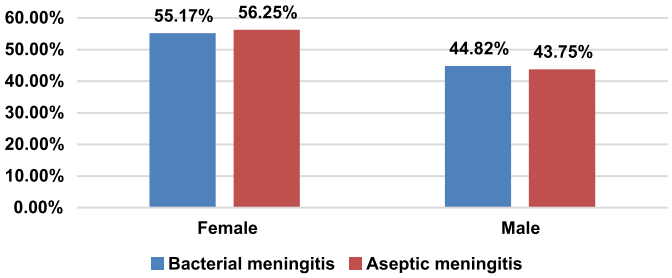

Figure 1: Gender Distribution of Bacterial and Aseptic Meningitis Study Patients

As illustrated in figure 2, according to the age groups, 18 (62.06%) bacterial meningitis, and 08 (50.0%) aseptic meningitis patients had an age between two to six years, while 11 (37.93%) bacterial meningitis and 08 (50.0%) aseptic meningitis patients had an age between seven to twelve years. The statistical association between gender, and age group with type of meningitis was estimated through the chi-square test. The present study found no statistically significant association between gender (p=0.597), and age groups (p=0.318) with types of meningitis. The p-value of <0.05 was considered statistically significant.

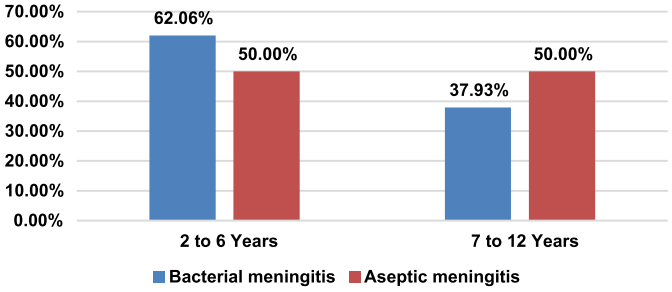

Figure 2: Age Group Distribution of Bacterial and Aseptic Meningitis Study Patients

Table 2 gives the picture of CRP values estimated in patients of bacterial and aseptic meningitis. The 20 (68.96%) bacterial meningitis and all aseptic meningitis patients had negative CRP (<3.0mg/L) while 9 (31.03%) bacterial meningitis patients had positive CRP (>3.0mg/L). The overall mean value of CSF-CRP was 2.216+1.697. The present study shows a statistically significant association between CSF-CRP results with bacterial and aseptic meningitis (p=0.003).

Table 2: CSF C-Reactive Protein Test Results in the Study Patients

CSF CRP Test Results	Bacterial Meningitis (n=29)		Aseptic Meningitis (n=16)		p-value (Chi-square)
	N (%)	Mean + SD	N (%)	Mean + SD	
CRP <3.0mg/L	20 (68.96%)	2.697 ± 1.9390	16 (100.0%)	1.344 ± 0.4211	0.003*
CRP >3.0mg/L	09 (31.03%)		0 (0.0%)		

*p-value is considered statistically significant.

DISCUSSION

In addition to being a frequent and dangerous infection in infancy and childhood, bacterial meningitis is a major contributor to child mortality and morbidity [15]. To prevent this, it is essential to identify the condition early and start treatment with a suitable drug [16]. In a nation with few resources like Pakistan, where it can be challenging and time-consuming to isolate organisms appropriately, a simple, fast, affordable, and accurate test is required. The present study was conducted to estimate the values of CSF-CRP in bacterial and aseptic meningitis patients. According to this study, CSF-CRP may be used in situations when it is challenging to isolate microbes. The findings from this hospital-based study showed that the age group most vulnerable to acute bacterial meningitis was young children. Most of the patients (60.0%) belonged to the 02-06 years of age group and were affected with bacterial meningitis. A study by Rahman *et al.*, also showed similar results [17]. The present study had a female preponderance (55.6%). The results of Bhatta *et al.*, study showed the male preponderance of meningitis patients [18]. The difference in results may be due to the population, and geographical differences. The study patients were mostly infected with bacterial meningitis (64.4%) as compared to aseptic meningitis (35.6%). The study conducted by Rahman *et al.*, enrolled 100 patients and showed that most patients were infected with bacterial meningitis (57.0%) [16]. Another cohort study conducted by Mintegi *et al.*, concluded that more patients were infected with aseptic meningitis (88.86%) [11]. In the present study, (68.96%) bacterial meningitis and all aseptic meningitis patients had negative CRP (<3.0mg/L) while the 09 (31.03%) bacterial meningitis patients had positive CRP (>3.0mg/L). The study by Rahman *et al.*, showed that (89.47%) of patients of bacterial meningitis, and 04 (6.97%) patients of aseptic meningitis had positive CSF-CRP [17]. According to Jadavinia *et al.*, patients with bacterial meningitis had statistically significantly greater levels of CRP in their CSF than those with aseptic meningitis. CRP value was 0.95±0.68 mg/L in septic and 0.16±0.36 mg/L in aseptic with statistically significant p<0.001 [19]. As per Jablr PM *et al.*, the mean CSF CRP values in cases of viral and bacterial meningitis were 3.16 and 4.44. They concluded that there was no difference (p=0.39) in the mean CSF CRP levels between viral and bacterial meningitis [20]. The present study shows a statistically significant association between CSF-CRP results with bacterial and aseptic meningitis (p=0.003). The overall mean value of CSF-CRP was 2.216 + 1.697. The mean value of CSF-CRP of bacterial meningitis was 2.697 + 1.9390, while the mean value of CSF-CRP of aseptic meningitis was 1.344 + 0.4211. According to Panji M *et al.*, the mean CRP of CSF was 55.22 ± 3.11 mg/L for bacterial meningitis and 7.5 ± 1.18 mg/L for aseptic meningitis. They also reported a statistically significant

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association (p=0.001) between CRP and meningitis [21]. The agglutination technique was used in this study to measure the CSF-CRP. Improved laboratory facilities might reduce the study's limitations by enabling the detection of hs-CRP concentrations in CSF samples.

CONCLUSIONS

The present study concluded that the CSF-CRP is associated with bacterial and aseptic meningitis. While awaiting the results of other confirmation tests, it can be utilized as an early diagnostic tool for the diagnosis of bacterial and aseptic meningitis. The current study also found that, in contrast to aseptic meningitis, bacterial meningitis had a considerably higher CSF-CRP level. Therefore, it could also aid in the early diagnosis of aseptic vs bacterial meningitis.

Authors Contribution

Conceptualization: UA, RSATK
Methodology: FA, MN
Formal analysis: UA, SP
Writing-review and editing: FA, OSKR, AR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Determining Efficacy of Intracanal Cryotherapy on Post Endodontic Pain in Irreversible Pulpitis

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ABSTRACT

Endodontic cryotherapy is a procedure that reduces pain and inflammation by applying cold to tissues, aiming to decrease post-endodontic pain. **Objectives:** To compare the effectiveness of cryo-treated endodontic irrigant in reducing post-endodontic pain in mandibular molars with irreversible pulpitis. **Methods:** This comparative analytical study was conducted from December 2023 to February 2024 in the Department of Operative Dentistry at Lahore Medical and Dental College. It included patients of both genders, aged 18 to 60, with symptomatic irreversible pulpitis in mandibular molars and pre-endodontic pain of VAS 7-10 for 10 days or less. Patients were divided into two groups: Group A (normal saline) and Group B (cryotherapy). Patients were instructed on using the Visual Analogue Scale (VAS) to assess pain. Group B received final irrigation with 20 ml normal saline at 2.5°C for 5 minutes, while Group A received 20 ml normal saline at room temperature. Pain scores were recorded preoperatively and at 24 and 48 hours' post-treatment via telephone interviews. Data were analyzed using SPSS version 25 and a repeated measures ANOVA test assessed VAS scores across time points. A p-value <0.05 was considered significant. **Results:** 45 (46%) were male and 53 (54%) were female patients, with mean age of patients being 35.71 ± 10.71years. At 24 hours postoperatively, the mean VAS score was 1.51 ± 1.2 for the normal saline group and 0.98 ± 0.9 for the cryo-treated saline group. By 48 hours postoperatively, the mean VAS score further decreased to 0.27 ± 0.5 for the normal saline group and 0.12 ± 0.4 for the cryo-treated saline group. The mean differences in VAS scores at 24 hours showed significant difference in mean pain score (P-value<0.05) but at 48 hours between the two groups showed no significant difference (p = 0.104). **Conclusions:** Both saline groups significantly decreased pain, the type of saline, normal or cryo-treated, did not significantly impact overall pain scores differently between the groups.

INTRODUCTION

Dental pain, particularly odontogenic pain, is the primary motivator for patients seeking dental treatment. Ironically, unresolved dental pain can lead patients to abandon their dental care. Therefore, dental practitioners prioritize treatment options that effectively alleviate pain [1, 2]. Literature has addressed a range of techniques and strategies for managing postoperative pain following endodontic operations [3]. Prescription drugs, intra-canal treatments and occlusal modifications are among these methods. However, each has its drawbacks. For instance, the use of Nonsteroidal Anti-Inflammatory Drugs (NSAIDs) has been linked to adverse effects on the stomach and liver. Additionally, there are conflicting findings in the literature regarding the efficacy of intra-canal therapies like calcium hydroxide, laser application and analgesic solutions in reducing postoperative endodontic discomfort [4, 5]. Cryotherapy, a recent therapeutic innovation, capitalizes on the application of low temperatures to stimulate healing and offer various therapeutic advantages [6, 7]. Its core mechanism triggers three primary tissue responses: vasoconstriction, inhibition of neural receptors and a reduction in metabolic activity. By limiting the release of

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pain-inducing chemical mediators and slowing the propagation of neural pain signals, cryotherapy effectively reduces postoperative pain. Cryotherapy additionally enhances the delivery of oxygen to injured tissues by drastically diminishing cellular metabolism, with potential reductions of up to 50% [8]. Cryotherapy is used in dentistry to treat a variety of disorders. In the field of endodontics, cryotherapy may be used in several settings. It can be used to lessen postoperative discomfort and inflammation after root canal procedures and after periradicular surgery [9]. Furthermore, with the use of bioceramic materials in conjunction with cryotherapy, cryotherapy has proven to be an efficient supplementary strategy for attaining hemostasis in crucial pulp cryotherapy in more recent times [10]. Cryotherapy is unique in that it is an easy, affordable, and safe alternative for managing endodontic pain. The rationale of conducting this study is to emphasis to include cryotherapy techniques in daily clinical endodontic practice, the potential benefits being significant [8]. This study underscores the effectiveness of cryotherapy, particularly when managing post endodontic pain. Todorova MV et al., in an in vitro study revealed that utilizing a saline solution at 5 mL for 5 minutes was insufficient for a cryotherapy affect [11]. At a capacity of 20 mL, the temperature difference between the initial and lowest recorded values was reached the quickest, at 10°C. This temperature drop may likely produce a localized anti-inflammatory impact in the peri-radicular area [6].

This study was to ascertain efficiency of decrease in post endodontic pain by using room temperature normal saline and cryo-treated saline, in irreversible pulpitis mandibular molars with no apical periodontitis.

METHODS

This comparative analytical study was conducted from December 2023 till February 2024, in the department of Operative Dentistry in Lahore Medical and Dental College. Approval was obtained from ethical committee (IRB) of the college, FD/5301/23. Patients included were of both genders, from 18 to 60 years of age, presenting with symptomatic irreversible pulpitis in mandibular molars, with pre-endodontic pain of VAS, from 7-10, for 10 days or less. It was also noted that there was no consumption of any analgesics or antibiotics, at least 7 days prior to the visit. To determine pulp sensitivity, an electric pulp tester was used to diagnose. Participants in the study were excluded whose teeth were determined to be necrotic, exhibit inadequate coronal tooth structure, required re-endodontic treatment, had severe periodontal disease, or had systemic conditions like diabetes or autoimmune illnesses. Using WHO calculator, sample size of 101 patients was determined with confidence level of 95%, power of test 90 and a population proportion of 80% and 61.14% for groups A and B, respectively, 51 were allotted to each group [8]. Individuals meeting the criteria were informed on the treatment and study design. After gaining consent of the patient, proformas were used to record patient information, such as age and gender. Regarding randomization, the foremost case was assigned to group A, second for group B, the next case for group A and so on, without disclosing to the participant the treatment group they were allotted. Group A was normal saline group and Group B was cryotherapy group. Patients were blinded to groups, but clinicians could not be, as temperature difference was felt through the 5cc plastic irrigation syringe. Both groups underwent pre-established procedures. Before treatment, patients were provided instructions on use of Visual Analogue Scale (VAS) to assess the pain. The VAS values 0 denoting no pain, 1-3 denoting mild pain, 4-6 denoting moderate pain and 7-10 denoting severe pain were explained to the patients. After determining the preoperative pain score, we used an inferior alveolar nerve block to deliver local anesthesia consisting of 2% lidocaine and 1: 100,000 epinephrine. After that, a rubber barrier was installed, and burs were used to get to the endodontic site. After access, working lengths were established using radiograph. Root canals were instrumented with a protaper hand files using copious 2.5% sodium hypochlorite irrigant. After complete instrumentation, root canals were flushed with 17% EDTA for 1 min. In cryotherapy group, final irrigation was done in root canals using 20 ml normal saline, for 5 minutes at 2.5°C temperature. Cryotreated saline was stored in a controlled refrigerator till use. Whereas in the normal saline group, 20 mL of normal saline at room temperature was used. In both groups, canals were dried using paper points and immediately obturated with single cone technique using gutta-percha cones and sealapex sealer. Coronal access cavities were temporized using glass ionomer cement. Participants were telephoned to inquire about their analgesic consumption and to document their VAS scores for 24-hour and 48-hour marks. If an analgesic was consumed, the patient was excluded from the study. This was to ensure that no decrease in VAS score occurred due to analgesic effect, on follow up VAS scores, but only due to the treatment provided to the patient. Data were inserted and analysed using SPSS version 25.0. Qualitative data for gender was displayed as frequency and percentages. Age and VAS scores means and standard deviations were used to display the quantitative data. Repeated measure ANOVA test was used to assess pain using the VAS at follow up and mean VAS scores in both saline groups at preoperative pain, 24 hours after surgery and 48 hours after treatment was compared by independent sample t test. P-value <0.05 was considered as significant.

RESULTS

Of the 102 participants enrolled, four were excluded from the results due to one drop out and three patients requiring analgesics within 24 hours, resulting in a total of 98 participants. 49(50%)were treated using normal saline and 49 were treated using cryotreated saline. Out of these 98 participants, 45 (46%) were males and 53 (54%) were

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females. Amongst males, those treated with normal saline were 19 (42%) and 26 (58%) were treated with cryotreated saline. Whereas 30 (57%) female patients were treated using normal saline and 23 (43%) were cryotreated. Mean age was 35.71 ± 10.71 years. Patients with age range from 18-40 years old were 67 (68%) and those of 41-60 age categories were 31(32%) as shown in table 1.

Table 1: Baseline Characteristics of Patients

Variables		Frequency (%)/ (Mean ± SD)
Gender	Male	45 (46%)
	Female	53 (54%)
Male Treatment	Normal Saline	19 (42%)
	Cryotreated Saline	26 (58%)
Female Treatment	Normal Saline	30 (57%)
	Cryotreated Saline	23 (43%)
Age Categories	18-40 Years	67
	41-60 Years	31
Mean Age (Years)	35.71 ± 10.71	

Table 2 showed mean and standard deviation of VAS scores for each group. Initial preoperative VAS scores were comparable between groups. Further examination of within subject's effects using ANOVA revealed significant reductions in VAS scores over time within each group ($p < 0.001$). An independent sample t-test comparing the mean differences in VAS scores at 24 hours showed significant difference in mean pain score but at 48 hours between the two groups showed no significant difference ($p = 0.104$). In conclusion, while time significantly influenced VAS scores, the type of saline used, did not significantly impact overall pain scores differently between the two groups.

Table 2: Comparison of Visual Analogue Scale (VAS) Scores Between Normal Saline and Cryotreated Saline Groups at Different Time Points

Groups	Visual Analogue Scale (VAS) Scores (Mean ± SD)			
	Pre-Operative	24 Hours	48 Hours	p-Value
Group A Normal Saline	8.47 ± 1.3	1.51 ± 1.2	0.27 ± 0.5	<0.001[a]
Group B Cryotreated Saline	8.73 ± 1.2	0.98 ± 0.9	0.12 ± 0.4	<0.001[a]
p-Value	0.306[b]	0.01[b]	0.104[b]	-

[a] = ANOVA
[b] = Independent sample t-test

DISCUSSION

A novel, cost effective method of treating patients seeking emergency care for endodontic pain may be able to lessen their postoperative pain, according to the results of our experimental clinical research. Most cryotherapy users assert that it has many advantages, such as decreased microbial activity, inflammation and postoperative pain [10]. Other research endeavors on the application of cold saline in endodontics have produced varying conclusions concerning its therapeutic consequences [12]. Compared to conventional techniques, a number of studies have indicated that cold saline irrigation during root canal therapy can successfully lower postoperative pain levels [13, 14]. This is due to vasoconstriction brought on by the cold causes a reduction in nerve transmission and pain perception [2]. By lowering the activation threshold of the tissue nociceptors and the velocity at which pain signals are conducted, cryotherapy produces a local anesthetic effect. According to Mohammadi *et al.*, cold saline irrigation has antimicrobial qualities because it inhibits the growth of bacteria and lowers the number of bacteria present in the root canal system [12]. This reduces the possibility of reinfection and may help with disinfection. Cryotherapy's ability to decrease post-endodontic pain in teeth presenting with irreversible pulpitis with or without apical periodontitis was compared in some randomized multicenter clinical trials. Bazaid DS stated that, only individuals with apical periodontitis responded to cryotherapy and among patients with irreversible pulpitis alone, there was no discernible variation in the prevalence of postoperative discomfort amongst the cryotherapy and control groups [15]. Alharthi AA *et al.*, in their randomized controlled study had similar results to ours in which they stated that in previously asymptomatic instances without periapical pathosis, room-temperature saline as the last irrigation produced outcomes that were comparable to intracanal cryotherapy [16]. Jamdar SF also stated that they had no significant differences in decrease of post op pain between groups [13]. All these studies are in accordance to our research as the inclusion criteria was limited to cases of irreversible pulpitis and we found the type of saline, normal or cryotreated, did not significantly impact overall pain scores differently between both the saline groups. Sadaf *et al.*, assessed impact of intracanal cryotherapy on postoperative pain following endodontics in both pulpal and periradicular pathosis through a systematic review [17]. The results demonstrated intracanal cryotherapy considerably decreased post-operative pain six hours and twenty-four hours following the treatment as compared to controls. After the operation, however, there was no discernible change in discomfort 48, 72, or 7 days later. In our study, temperature of saline normal room or cryotreated did not significantly affect total pain scores differently across the two saline groups, though there was significant decrease in VAS scores over 24 and 48 ours postoperatively. In their meta-analysis, Monteiro LP *et al.*, found that there was less postoperative pain six and twenty-four hours following cryotreated irrigation [18]. Patients who received intracanal cryotherapy showed a decrease in postoperative pain levels on the seventh day when compared to the room temperature group, albeit this difference did not reach statistical significance. Our research produced conflicting findings to this but was in accordance to Gupta A *et al.*, and according to Gupta *et al.*, systematic analysis, intracanal cryotherapy did not

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significantly reduce post endodontic pain, which is in line with our investigation's results [10]. Using EndoVac has been demonstrated to decrease the probability of periapical inflammatory reactions by minimizing apical extrusion [7]. All patients in this research had root canal therapy using traditional needle irrigation needle that was inserted 2 mm short of working length. It has been demonstrated that negative apical pressure devices produce less postoperative pain and considerably less irrigant extrusion than conventional needle irrigation [19]. Therefore, as advised by earlier research, the needle was not placed more than 2 mm from the working length in order to provide a safe irrigation routine. There was significant decrease in VAS score in our study, in spite of using traditional needle irrigation. Although an ideal protocol for volume and length of time for intracanal cryotherapy is yet to be established, majority of the studies employed 20 mL of cold saline for five minutes at 2.5°C [15, 20]. For locations with minor fat or muscle, such the fingers, 3-5 minutes of cold treatment is thought to be sufficient, as opposed to 20 minutes, which is advised for regions with deep tissues, like the hips [21]. Nevertheless, extending these findings to root canal treatment may be, at most, speculative. Thus, it should be a top priority to conduct additional research to determine the ideal dosage and duration. Another limitation of the study includes that double blinding could not be done as temperature difference of cryotreated saline could be felt through the plastic irrigation syringes. The results of our analysis demonstrated that the randomization process and the large sample size employed in the study had enabled the normal temperature saline and cryotreated saline to have similar distributions of variables.

CONCLUSIONS

In summary, cryotherapy and normal saline resulted in a reduction in the occurrence of postoperative pain, in patients diagnosed with irreversible pulpitis.

Authors Contribution

Conceptualization: AFB
Methodology: UWJ
Formal analysis: MUDA, MTK
Writing, review and editing: AFB, SRK, AAB

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Effects of Adrenaline Containing Local Anesthesia on Blood Pressure and Blood Glucose Levels Undergoing Tooth Extractions – A Comparative Study

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ABSTRACT

Exodontia, the most common dental procedure for damaged or decayed teeth, often utilizes local anesthesia with vasoconstrictors like adrenaline. Although effective, adrenaline can impact blood glucose levels and hemodynamic parameters, particularly in hypertensive and diabetic patients. **Objectives:** To compare changes in blood pressure and blood glucose levels among healthy, hypertensive and diabetic patients undergoing tooth extraction with adrenaline-containing local anesthesia. **Methods:** A total of 177 participants were split equally into three groups: healthy, hypertensive and diabetic. Prior to and twenty minutes' post-injection, blood pressure, and blood glucose levels were measured while a local anesthetic containing 2% lignocaine HCL with 1: 100,000 adrenaline was administered. Sample paired t test and one-way ANOVA were employed in the analysis. **Results:** After the procedure, hypertensive patients experienced a significant decrease in random blood glucose levels (p=0.001). Similarly, systolic blood pressure exhibited a significant increase (p<0.001), while diastolic blood pressure significantly decreased (p=0.021), post-procedure. Diabetic patients showed a non-significant decrease in glucose levels (p=0.209) but a significant increase in both systolic (p<0.001) and diastolic blood pressure (p=0.002). Healthy patients experienced a significant increase in systolic blood pressure (p=0.015) but no significant changes in glucose levels (p=0.873) or diastolic pressure (p=0.301). **Conclusions:** Adrenaline in local anesthesia significantly increases systolic blood pressure in all patient groups, with pronounced effects in hypertensive and diabetic patients. Changes in blood glucose were significant only in hypertensive patients, while changes in diabetic patients were non-significant. These findings highlight the need for careful monitoring and personalized management strategies in dental procedures to minimize potential adverse effects and ensure patient safety.

INTRODUCTION

Exodontia is indeed the most common dental procedure performed when a tooth is damaged, infected, or decayed [1]. While it is considered a routine procedure, it can still be stressful and uncomfortable for many patients [2]. Local anesthesia is the primary method used in dentistry to minimize intraoperative pain and discomfort while performing dental procedures. It is typically administered with vasoconstrictors, which are considered safe and are commonly used in dental practices [3, 4]. The inclusion of vasoconstrictors provides several advantages, such as enhancing the local anesthetic effect, improving hemostasis, and reducing systemic toxicity [5]. However, it is documented that adrenaline, a common vasoconstrictor, can impact hemodynamic parameters and blood glucose levels. Specifically, adrenaline can increase heart rate and blood pressure through vasoconstriction and stimulate glycogenolysis and gluconeogenesis, while decreasing glucose utilization by tissue [6-10]. Given the high prevalence of hypertension and diabetes worldwide, these conditions are frequently encountered in patients visiting dental clinics [11, 12]. Therefore, it is crucial for dental professionals to

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understand how to effectively manage and treat patients with hypertension and diabetes during dental procedures. Controversy remains in the use of local anesthesia containing epinephrine in hypertensive patients due to its effect on beta 1, beta 2 and alpha receptors [13]. The systemic absorption of epinephrine can lead to unexpected cardiovascular effects, such as severe hypertension and ventricular arrhythmias, emphasizing the need for caution when using epinephrine in local anesthesia [12]. The observed increase in systolic and diastolic pressure is primarily dependent on the plasma clearance of exogenous epinephrine. Hypertensive emergencies during dental treatment can lead to life-threatening situations [7]. The increase in glucose levels after local anesthesia with adrenaline is due to adrenaline's vasoconstrictive effects, which reduce the systemic absorption of the anesthetic, leading to higher blood concentrations [8, 14]. Studies show that diabetic patients not on hypoglycemic medication experience significant blood glucose increase after receiving adrenaline-containing anesthesia for tooth extraction [15]. Stress and discomfort can significantly raise glucose concentrations, emphasizing the impact of stress on blood sugar levels. The relationship between stress levels and blood sugar levels in individuals with diabetes mellitus highlights a strong positive correlation, indicating that stress can complicate glycemic control in diabetic patients [16].

This study aimed to compare blood pressure (both systolic and diastolic) and blood glucose levels among healthy, hypertensive and diabetic patients pre and post tooth extraction with local anesthesia containing adrenaline as vasoconstrictor.

METHODS

The observational comparative study involved 177 participants, conducted at the Oral and Maxillofacial Department at the University College of Dentistry, The University of Lahore, following approval from the university's ethical committee on 14-03-2023 with reference number UCD/164 between June 2023 to September 2023. A purposive sampling technique was employed to select participants based on specific criteria. This non-probabilistic method was chosen to specifically include individuals who met the predefined inclusion and exclusion criteria, ensuring the sample's relevance and alignment with the study's objectives. The calculated sample size was 18 (6 in each group) with 95% confidence level, 80% power of test and by taking expected mean value of post-op blood sugar level for healthy and diabetic patients as 102.97 ± 14.7 and 202.47 ± 54.45 respectively [17]. Given the variability in individual responses to dental anesthesia and the importance of detecting even small differences in glycemic response, a larger sample size of 59 participants per group was chosen to increase the robustness and reliability of the findings. All participants had dental appointments between 9:00 AM to 11:00 AM at for extraction at the dental hospital. Medical history and written informed consent were obtained from all patients. The study consisted of three groups: Group A, comprising healthy patients; Group B, consisting of hypertensive patients who were managing their condition with medication and Group C, including diabetic patients who were managing diabetes through either oral hypoglycemic agents or insulin. All patients were priorly diagnosed by their respective physicians according to international guidelines for their respective conditions and treated accordingly. For blood pressure measurement, a sphygmomanometer and stethoscope were used, while for blood glucose concentration, an Accu-Chek instant glucometer (mg/dl), sterile lancets and a lancing device were used. The inclusion criteria for healthy patients are as follows: patients should not have any systemic disorders and should not be taking any medication for any other ailment. In the case of hypertensive patients, the study included those who were managing their condition with medication and dietary restrictions. Likewise, diabetic patients who were managing diabetes through dietary control and medication such as insulin or oral hypoglycemic agents were included in the study. The exclusion criteria comprise pediatric extractions, patients who received local anesthesia without adrenaline or required more than one cartridge of 1.8ml of local anesthesia, pregnant patients, surgical extractions and patients with uncontrolled diabetes and blood pressure without undergoing treatment. After explaining the procedure to the patient, the healthcare provider proceeded to assess the patient's blood pressure and random blood glucose level. Blood pressure was measured using a stethoscope and sphygmomanometer according to standard clinical practice. The cuff was placed snugly around the upper right arm and the pressure was gradually increased until it temporarily cut off blood flow. As the pressure was released, the demonstrator listened for the characteristic sounds using the stethoscope placed over the brachial artery. The systolic pressure was recorded at the onset of these sounds and the diastolic pressure was recorded when the sounds disappeared. For blood glucose measurement, the finger (from which blood was to be taken) of the patient was cleaned with sterile alcohol gauze. The blood drop was then obtained by pricking the sterile lancet over the finger and placing the strip on the glucometer, using an Accu-Chek glucometer. Subsequently, the blood pressure readings and blood glucose levels were documented on the patient's record form at the start of the procedure and 20 minutes after injecting one cartridge of the local anesthesia. All the above procedure was performed by a trained demonstrator. The extraction procedure was carried out by injecting local anesthetic 2% lignocaine HCL (1.8ml) cartridge with 1:100,000 adrenaline either as an Inferior Alveolar Nerve (IAN) block or as an infiltration depending on the tooth to be extracted. Teeth were extracted using atraumatic techniques. Blood pressure and plasma

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glucose levels were tested and recorded prior and 20 minutes after the injection. Data entry and analysis were done with SPSS version 25.0. Quantitative variables were presented with mean ± SD and qualitative variables with frequency and percentages. To compare random blood glucose, systolic and diastolic blood pressure before and after (local anesthesia with adrenaline) within study groups, a paired sample t-test was applied. The comparison of blood glucose levels, systolic and diastolic blood pressure between groups after the procedure was conducted using one-way ANOVA. A p-value equal to or less than 0.05 was considered statistically significant.

RESULTS

The study comprised 177 participants, divided into three groups: Healthy (n=59), Hypertensive (n=59) and Diabetic (n=59). The Healthy group had a mean age of 47.23 ± 15.15, spanning from 20 to 81 years. The mean age of participants in the Hypertensive group was 65.55 ± 4.05 years, ranging from 60 to 70 years. In the Diabetic group, the mean age was 54.67 ± 8.92 years, with an age range of 37 to 69 years. Gender distribution varied among the groups, with the majority being female in two groups as 66.1% in the Hypertensive group followed by 52.2% in the Diabetic Group. The demographic characteristics of the participants are summarized in table 1.

Table 1: Demographics of Study Participants

Variables	Healthy (N=59)	Hypertensive (N=59)	Diabetic (N=59)
Age	**Mean ± SD**		
	47.23 ± 15.15	65.55 ± 4.05	54.67 ± 8.92
	Min-Max		
	20-81	60-70	37-69
Gender	**Male N (%)**		
	35 (59.3%)	20 (33.9%)	28 (47.5%)
	Female N (%)		
	24 (40.7%)	39 (66.1%)	31 (52.5%)

Table 2 displayed the results of the paired sample t-test conducted to assess changes in random blood glucose levels and blood pressure among the three groups of patients 20 minutes' post-injection. Among hypertensive patients, a significant decrease was observed in random blood glucose levels (p=0.001), while systolic blood pressure significantly increased (p<0.001) and diastolic blood pressure significantly decreased (p=0.021) post-procedure. In diabetic patients, a non-significant decrease was noted in blood glucose levels post-procedure (p=0.209), while both systolic (p<0.001) and diastolic blood pressure (p=0.002) exhibited a significant increase. Conversely, among healthy individuals, no significant changes were observed in random blood glucose levels (p=0.873) or diastolic blood pressure (p=0.301) post-procedure compared to pre-procedure values. However, there was a significant increase in systolic blood pressure post-procedure compared to pre-procedure levels (p=0.015) as shown in table 2.

Table 2: Random Blood Glucose Level (BGL), Systolic (SBP) and Diastolic Blood Pressures (DBP) in Study Groups before and after Procedure

Groups	Variables	Pre and Post Treatment	Mean ± SD	Difference Pre and Post (Mean ± SD)	p-Value
Healthy	BGL (mg/dL)	Pre-Treatment	124.10 ± 31.94	0.71 ± 33.92	0.873
		Post-Treatment	123.38 ± 29.27		
	SBP (mmHg)	Pre-Treatment	124.57 ± 13.82	7.20 ± 22.10	0.015*
		Post-Treatment	131.77 ± 18.10		
	DBP (mmHg)	Pre-Treatment	79.10 ± 8.47	2.77 ± 13.03	0.107
		Post-Treatment	81.88 ± 9.44		
Hypertensive	BGL (mg/dL)	Pre-Treatment	121.37 ± 25.041	-7.76 ± 16.97	0.001*
		Post-Treatment	13.61 ± 29.23		
	SBP (mmHg)	Pre-Treatment	142.03 ±7.88	10.00 ± 7.54	<0.001*
		Post-Treatment	152.03 ± 8.10		
	DBP (mmHg)	Pre-Treatment	83.98 ± 9.08	-2.20 ± 7.14	0.021*
		Post-Treatment	81.77 ± 4.71		
Diabetic	BGL (mg/dL)	Pre-Treatment	183.62 ± 41.77	7.33 ± 44.40	0.209
		Post-Treatment	176.28 ± 50.92		
	SBP (mmHg)	Pre-Treatment	124.57 ± 18.011	16.77 ± 18.11	<0.001*
		Post-Treatment	41.35 ± 18.35		
	DBP (mmHg)	Pre-Treatment	76.52 ± 8.16	4.66 ± 10.98	0.002*
		Post-Treatment	81.18 ± 5.74		

*Significant p-value

Table 3 presents the results of the one-way ANOVA conducted to assess differences in random blood glucose levels and blood pressure among the study groups (Healthy Control, Hypertensive and Diabetic). A significant difference was observed between study groups for both random blood glucose levels (p<0.001) and systolic blood pressure (p<0.001). However, diastolic blood pressure did not show any significant difference between the study groups (p=0.842) as shown in table 3.

Table 3: Comparison of Random Blood Glucose Level (BGL), Systolic (SBP) and Diastolic Blood Pressure (DBP) between Study Groups after Procedure

Variables	Groups	Mean ± SD	Standard Error	p-Value
BGL (mg/dL)	Healthy	123.38 ± 29.27	3.81	<0.001*
	Hypertensive	113.61 ± 29.23	3.80	
	Diabetes	176.28 ± 50.92	6.63	
SBP (mmHg)	Healthy	131.77 ± 18.10	2.35	<0.001*
	Hypertensive	152.03 ± 8.10	1.05	
	Diabetes	141.35 ± 18.35	2.38	
DBP (mmHg)	Healthy	81.88 ± 9.44	1.22	0.842
	Hypertensive	81.77 ± 4.71	0.61	
	Diabetes	81.18 ± 5.74	0.74	

*Significant p-value

Table 4 illustrated that there was no significant difference in random blood glucose levels and systolic blood pressure among patients using oral diabetic medication and insulin pre and post-procedure, respectively. However, a significant difference was observed in diastolic blood pressure between oral and insulin user's pre and post-

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injection, respectively. This finding suggests a differential impact of oral medication and insulin on diastolic blood pressure in patients undergoing the procedure as shown in table 4.

Table 4: Comparison of Random Blood Glucose level (BGL), Systolic (SBP) and Diastolic Blood pressure (DBP) among Diabetic Patients in Relation to type of Medication.

Variables	Pre and Post Treatment	Oral Hypoglycemic N=41	Insulin N=18	p-Value
		(Mean ± SD)		
BGL (mg/dL)	Pre-Treatment	178.56 ± 29.72	195.17 ± 60.60	0.282
	Post-Treatment	174.37 ± 49.00	180.67 ± 56.30	0.666
SBP (mmHg)	Pre-Treatment	127.56 ± 17.43	117.78 ± 17.92	0.054
	Post-Treatment	146.22 ± 16.57	130.28 ± 17.78	0.002*
DBP (mmHg)	Pre-Treatment	78.90 ± 7.54	71.11 ± 6.98	<0.001*
	Post-Treatment	79.51 ± 5.22	85.00 ± 5.14	<0.001*

*Significant p-value

DISCUSSION

Previous studies have presented conflicting findings regarding the impact of local anesthesia containing adrenaline on blood glucose levels and blood pressure in patients undergoing dental treatment. In the present study, we evaluated changes in random blood glucose and diastolic and systolic values before and after tooth extraction in healthy, hypertensive and diabetic patients using local anesthesia with adrenaline as a vasoconstrictor, to assess the association between blood pressure and hyperglycemia. In healthy individuals, adrenaline-induced hyperglycemia triggers compensatory mechanisms that result in a slight increase in glucose levels. However, in uncontrolled diabetic patients, these mechanisms are altered, leading to a marked accentuation of hyperglycemia. This is due to changes in hepatic glucose output and insulin-stimulated glucose utilization [18]. Interestingly, in the present study, a statistically significant decrease in the mean random blood glucose level was observed in the hypertensive group 0.873(p=0.01), while healthy controls exhibited a non-significant difference in mean random blood glucose levels pre and post injection (p=0.873). Diabetic patients whether on oral hypoglycemic agents or insulin, also exhibited a statistically non-significant difference in mean random blood glucose levels (p=0.209), consistent with findings reported by Khawaja NA *et al.*, but contrary to results reported by Nair VS *et al.*, Kaur P et al., Saad TA, Ahmad T *et al.*, Bhoosreddy S *et al.*, where increases in values were observed in controlled diabetic patients [8, 15, 19-22]. These findings contribute to the understanding of the complex interplay between adrenaline, blood glucose levels and patient health status. Epidemiological studies have consistently shown that hypertension is more prevalent among diabetic mellitus patients compared to the general population [23]. Moreover, higher blood pressure levels are associated with an increased risk of hyperglycemia, even in individuals without diabetes [24]. Hyperinsulinemia, often seen in individuals with insulin resistance, can lead to impaired insulin vasodilatory responses in peripheral tissues. This, in turn, increases vasoconstrictor responses to certain vasopressors, contributing to elevated systolic blood pressure levels [25-26]. In our study, healthy group, there was a significant increase in systolic blood pressure (p<0.001), but no significant changes were observed in random blood glucose levels or diastolic blood pressure post-procedure compared to pre-procedural values (p=0.842, 0.107, respectively). However, diabetic patients showed a significant increase in systolic blood pressure, with mean values rising by 16.77 ± 18.11 (pre vs post, p=0.001), followed by the hypertensive group which had an increase of 10.00 ± 7.54 (pre vs post, p=0.001). These findings align with those reported by Ali FM *et al.*, but another study showed the systolic and diastolic blood pressure remained constant after local anesthetic with vasoconstrictor, regardless patient's hypertensive profile or anxiety levels [27, 28]. However, Guimaraes CC *et al.*, meta-analysis showed that there was a decrease in systolic blood pressure after local anesthesia with a vasoconstrictor [29]. A compensatory increase in systolic blood pressure within the normal range was observed in the healthy group (p=0.015). This finding aligns with a study by Moaddabi A *et al.*, which attributed the increase to adrenaline-induced vasoconstriction and the body's stress response releasing catecholamines. Additionally, the delayed absorption of the anesthetic from the injection site prolonged its effects, contributing to elevated blood pressure [30]. However, this result contrasts with a study by Ali FM *et al.*, who did not find any change in normotensive patients after injecting adrenaline-containing local anesthesia [27]. Regarding diastolic blood pressure, diabetic patients experienced a significant increase, with mean values rising by 4.66 ± 10.98 (pre vs post, p=0.002). These are similar to findings in literature which may be due to their altered cardiovascular physiology, heightened sympathetic response, individual variation, and interactions with diabetes medications [6, 18]. Conversely, in this study, hypertensive patients on medication showed a significant decrease in diastolic blood pressure, with mean values dropping by 2.20 ± 7.14 (pre vs post, p=0.021). This can be attributed to the dominant effects of antihypertensive medications, reduced vascular resistance, and a blunted sympathetic response. The interaction between these factors and the physiological response to adrenaline leads to a net decrease in diastolic pressure [13, 26]. In exploring the association between blood pressure, hyperglycemia and the use of adrenaline in local anesthesia, our study provides valuable insights into the physiological responses of patients during dental procedures. The observed changes in random blood glucose and blood pressure levels underscore the importance of considering individual patient characteristics and medical history when administering dental anesthesia. Moreover, our findings raise intriguing questions about the underlying

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mechanisms driving these responses, warranting further investigation. By deepening our understanding of these dynamics, we can enhance patient safety and optimize treatment outcomes in dental practice

CONCLUSIONS

Our study demonstrates that adrenaline-containing local anesthesia used during tooth extraction affects blood pressure and blood glucose levels, with notable variations among healthy, hypertensive and diabetic patients. Adrenaline was associated with a significant increase in systolic blood pressure in all groups, particularly in hypertensive and diabetic patients. However, changes in random blood glucose levels were only significant in the hypertensive group. These findings suggest that while adrenaline effectively prolongs anesthetic effects and improves hemostasis, its impact on hemodynamic and glycemic parameters necessitates careful monitoring. Therefore, dental practitioners should adopt personalized management strategies to minimize potential adverse effects and enhance patient safety.

Authors Contribution

Conceptualization: IUR, MZ
Methodology: IUR, MZ, TFT
Formal analysis: IUR, MAA, TFT, KS, HK
Writing, review and editing: MAA, AK, HK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Assessment of Complete Remission Rate in Patients with Acute Myeloid Leukemia Undergoing 7+3 Induction Chemotherapy

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ABSTRACT

Acute leukemia is a fast-growing, overpopulated clone of immature proliferating cells that largely predominate in the bone marrow and have the capacity to prolong life indefinitely. Upon inspection and cytologic assessment of bone marrow or peripheral blood, the cells demonstrate quantified uncertainties. **Objective:** To determine the frequency of complete remission after induction 7+3 chemotherapy in patients with acute myeloid leukemia. **Methods:** The nature of this study was cross sectional study at Department of Oncology, Pakistan Institute of Medical Sciences, and Islamabad from 26 November, 2022 to 26 May, 2023. The hospital's laboratory fulfilled the complete blood count and provided the confirmed baseline bone marrow biopsy reports. All patients who were admitted received treatment with a 7+3 regime, a standard treatment protocol for all the adolescents and adults admitted. Every patient was prescribed for 7+3 induction therapy regimen which consists of 200 mg/m^2 cytarabine for seven days and idarubicin for three days, 12 mg/m^2 on the 1st, 3rd and 5th day. **Results:** The complete remission estimated turns out to be 61.1% and rest need further treatment. The average age of the patients was 48.56 ± 6.91 years. The mean BMI stood at 24.46 ± 1.49 kg/m^2 gender wise, 74 were male and 21 were female. Our mean CR was 61.1% that is 58 participants all the complete demographic is available. **Conclusions:** This study revealed a Complete Remission (CR) rate of 61.1% in patients with AML undergoing 7+3 induction chemotherapy. However, our findings suggest that older age is associated with lower CR rates, highlighting the need for tailored treatment strategies that balance efficacy with the potential risks of intensive therapies in this population.

INTRODUCTION

Acute myeloid leukemia is one of the most challenging diseases in the field of hematologic malignancies. AML is characterized by exponential production of atypical myeloid pro-founding cells in bone marrow as well as peripheral blood. Acute myeloid leukemia is an aggressive malignancy caused by mutations in developing hematopoietic stem cells that disrupt their differentiation and cause the accumulation of inadequate myeloid progenitors [1, 2]. The etiology and risk factors of AML are multifactorial; exposure to radiation, using cytotoxic chemotherapy, specific genetic syndromes, environmental and industrial hazards, and infection with specific blood-borne viruses [3]. Despite all these circumstances, AML had been diagnosed in 20,830 new cases, with more than 10,000 victims, in the US alone in 2015 [4]. The incidence of AML increases with age. There are about 13 cases per million under 65 years which increases to 122 per million in elder population [5]. Acute myeloid leukaemia accounts for 31.25% of all leukaemias in Pakistan, and it is more prevalent in males [6]. Clinically, extra medullary involvement may occur with signs such as hepatosplenomegaly, lymphadenopathy or infiltration of the skin. Diagnosis of AML includes examination of the peripheral blood smear, cytogenetic analysis, aspiration

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and biopsy of the bone marrow with subsequent molecular testing of cytogenetic changes. It is necessary to determine the subtype of the disease and evaluate the prognosis [7]. Currently, despite the advances in understanding the pathogenesis of the disease, as well as the emergence of new drugs in the treatment, this pathology can be difficult to treat, especially in elderly and high-risk patients [8]. Standard induction chemotherapy remains the most popular in the treatment of such patients, which involves the use of cytarabine in combination with an anthracycline with the subsequent goal of preventing a relapse. Among its varied use in recent years, 7 days of cytarabine administration combined with 3 days of an anthracycline has become accepted due to its effectiveness in achieving remission. Therefore, 7+3 induction remains standard therapy for AML patients [9, 10].

This study aimed to determine the remission rate in patients with AML who are undergoing 7+3 induction. This topic has many gaps in current research, and the study of efficacy will provide information for clinical decision-making. Systems analysis for the identification of factors affecting remission will be generated.

METHODS

The approval of study was taken from the College of Physicians and Surgeons Pakistan (CPSP) (CPSP/REU/ONC-2020/042-275). It was also reviewed and approved by the hospital's research ethics committee. This cross sectional study took place in the Department of Oncology, Pakistan Institute of Medical Sciences, Islamabad, from 26 November 2022 to 26 May, 2023. The sample size calculation was conducted using the WHO sample size calculator, with the following parameters: a confidence level of 95%, an anticipated population percentage of 61.66%, and a needed absolute precision of 5% [18]. As a result, a total of 95 patients diagnosed with AML were included in the study. Sampling methodology used was non-probability consecutive sampling. The inclusion criteria consisted of patients who had a confirmed diagnosis of AML and were considered appropriate candidates for 7+3 induction therapy. The criteria applied to individuals of any gender, between the ages of 15 and 55 years and informed written consent was taken from participants. The exclusion criteria included patients with acute promyelocytic leukaemia, chronic systemic illnesses such as decompensated heart failure, renal and liver failure, and hypersensitivity to any component of the medication regimen. A comprehensive Complete Blood Count (CBC) was conducted in the hospital laboratory, and initial bone marrow biopsy records were obtained for each participant. Afterwards, all patients who had registered were administered 7+3 induction therapy, which involved receiving cytarabine at a dosage of 200 mg/m2 for seven days and idarubicin at a dosage of 12 mg/m2 twice daily for three days. The follow-up was planned at 28th day. The evaluation of treatment response, particularly complete remission was labelled as per following operational definition, which was assessed on the 28th day after chemotherapy for all patients who had 7+3 induction therapy for Acute Myeloid Leukaemia (AML). This evaluation encompassed a comprehensive analysis of the blood components and a procedure to extract and examine the bone marrow tissue. Complete remission is defined as having 5% or less bone marrow blasts, no circulating blasts or blasts with Auer rods, no extra medullary illness, an Absolute Neutrophil Count (ANC) of at least 1.0 × 109/L (1000/µL), and a platelet count of at least 100×109/L (100,000/µL). The demographic parameters and study conclusions were documented. Data were entered and analysed using SPSS version 20.0. Age and BMI were descriptively analysed using mean and standard deviation. Frequencies and percentages were calculated for qualitative characteristics including gender and full remission. The stratification was used to adjust for effect modifiers such as age, gender and BMI. Post-stratification chi-square test was used, with p-value ≤ 0.05 indicating statistical significance.

RESULTS

The demographic characteristics of the study participants were as follows. The mean age was 48.56 years with a standard deviation of 6.91. The mean BMI was 24.46 kg/m2 with a standard deviation of 1.49. In terms of age distribution, 51 participants (53.7%) were under 50 years old, while 44 participants (46.3%) were over 50 years old. Gender distribution indicated that 74 participants (77.9%) were male, while 21 participants (22.1%) were female in table 1.

Table 1: Demographic Characteristics of Study Participants

Variables	Mean ± SD / N (%)
Age (Years)	48.56 ± 6.91
BMI (Kg/m2)	24.46 ± 1.49
< 50 Years	51 (53.7%)
> 50 Years	44 (46.3%)
Male	74 (77.9%)
Female	21 (22.1%)

In our study, 58 participants achieved complete remission, accounting for 61.1% of the total study population as shown in table 2.

Table 2: Frequencies and Percentages for Complete Remission

Complete Remission	N (%)
Achieved	58 (61.1%)
Not Achieved	37 (38.9%)
Total	95 (100.0%)

In table 3, stratification of complete remission by age groups was conducted. Among participants under 50 years

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old, 30 achieved complete remission (51.7%), while 28 achieved it in the group over 50 years old (48.3%). Overall, out of 95 participants, 58 achieved complete remission. The p-value for the comparison between age groups was 0.631, indicating no statistically significant difference in complete remission rates between the two age groups as shown in table 3.

Table 3: Stratification of Complete Remission with Age Groups

Complete Remission	Age Groups		Total N (%)	p-Value
	≤ 50 Years N (%)	> 50 Years N (%)		
Achieved	30 (51.7%)	28 (48.3%)	58 (100.0%)	0.631
Not Achieved	21 (56.8%)	16 (43.2%)	37 (100.0%)	
Total	51 (53.7%)	44 (46.3%)	95 (100.0%)	

In table 4, complete remission was stratified by gender. Among male participants, 48 achieved complete remission (82.8%), while 10 achieved it among female participants (17.2%). Overall, out of 95 participants, 58 achieved complete remission. The p-value for the comparison between genders was 0.153, indicating no statistically significant difference in complete remission rates between males and females as shown in table 4.

Table 4: Stratification of Complete Remission with gender

Complete Remission	Gender		Total N (%)	p-Value
	Male N (%)	Female N (%)		
Achieved	48 (82.8%)	10 (17.2%)	58 (100.0%)	0.153
Not Achieved	26 (70.3%)	11 (29.7%)	37 (100.0%)	
Total	74 (77.9%)	21 (22.1%)	95 (100.0%)	

In table 5, complete remission was stratified by BMI. Among participants with a BMI less than 25 kg/m^2, 28 achieved complete remission (48.3%), while 30 achieved it among those with a BMI greater than 25 kg/m^2 (51.7%). Overall, out of 95 participants, 58 achieved complete remission. The p-value for the comparison between BMI groups was 0.583, indicating no statistically significant difference in complete remission rates between participants with BMI less than 25 kg/m^2 and those with BMI greater than 25 kg/m^2 as shown in table 5.

Table 5: Stratification of Complete Remission with BMI

Complete Remission	BMI		Total N (%)	p-Value
	≤ 25 Kg/m^2 N (%)	> 25 Kg/m^2 N (%)		
Achieved	28 (48.3%)	30 (51.7%)	58 (100.0%)	0.583
Not Achieved	20 (54.1%)	17 (45.9%)	37 (100.0%)	
Total	48 (50.5%)	47 (49.5%)	95 (100.0%)	

DISCUSSION

Acute Myeloid Leukemia is one of the most difficult malignancies in oncology, characterized by high morbidity rates and varied responses to treatment. One of the cornerstone treatment regimens is 7+3 induction chemotherapy, which comprises cytarabine and an anthracycline, used to achieve remission. However, despite high success rates, this approach is associated with adverse events of myelosuppression and complications of infections, which requires special attention to the supportive care. Future research aims at optimization of the 7+3 induction, and discovery of new strategies for the optimization of patient outcomes undergoing treatment with induction chemotherapy [11, 12]. In the present study, the mean age was 48.56 ± 6.91 years; among participants, 53.7% were under 50 years, and 46.3% were over 50 years. The gender distribution demonstrated a majority of males (77.9%). These findings correlate with those obtained by previous researchers, such as Ciftciler R *et al.*, who found a median age of 45 years at the time of diagnosis and a similarly male-associated tendency [13]. In another research, with the relatively low median age of 44 years and male predominance in sex distribution, reported similar results for their study cohort [14]. However, in contrast with our data, Shireen I *et al.*, indicated a lower mean age of 35.02 and a higher response to induction in a male population. The divergence referred above might have been predetermined by the differences in AML pattern within that particular population and health care provision settings [15]. Zaki S *et al.*, presented a young mean age of 27.5 and a balanced sex distribution, corresponding to our findings [16]. This study focused on the relationship between gender and complete remission rate among participants receiving 7+3 induction chemotherapy for AML. The findings showed that the proportion of complete remission among males was 82.8% and 17.2% among the females. This conclusion agrees with the report in a study by Shireen I *et al.*, who found that males were more responsive to induction therapy of patients under 40 years [15, 16]. A country study under Perera RA *et al.*, conducted in Srilanka reported that the rate of CR was 50% among patients with AML. The difference could be attributed to the type of patients, protocol, and health care system [17]. Abuelgasima KA *et al.*, have also designed a retrospective analysis that showed 61.66% complete remission rate in the 7+3 regimen patients. The established complete remission rate differed depending on the age group. Thus, it had a peak of 71.42% in the 14-40-year-old patients while the lowest remission rate of 45.47% was observed in the patients older than 60-year-old [18]. Yoon JH *et al.*, have analyzed the complete remission among the standard 7+3 induction patients in Korea. Although their overall complete remission rate was similar to the finding of this study, they identified no age-related changes, as their non-significant difference in the rates was found between the <55-years old and ≥55-years old patients [19]. Therefore, the complete remission rates in the 7+3 induction patients with AML show some differences between the male and female subjects, which are consistent with Hadisantoso DW *et al.*, however, this pattern requires further experimental validation and clinical consideration for the optimization of the treatment strategy [20].

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CONCLUSIONS

This study revealed a Complete Remission (CR) rate of 61.1% in patients with AML undergoing 7+3 induction chemotherapy. However, our findings suggest that older age is associated with lower CR rates, highlighting the need for tailored treatment strategies that balance efficacy with the potential risks of intensive therapies in this population.

Authors Contribution

Conceptualization: NM, AK
Methodology: NM, AK, AA, SA, MT
Formal analysis: AM
Writing, review and editing: AA, SA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Clinical Effectiveness of Benzoyl Peroxide and Clindamycin Combination Therapy in the Treatment of Papulopustular Acne

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ABSTRACT

Acne is a prevalent inflammatory skin condition affecting 9% of the global population. Its impact on quality of life and self-esteem leads to depression and anxiety. Combination regimen may be effective in treating acne. **Objective:** To assess the clinical effectiveness of a fixed-dose combination of 1% clindamycin and 5% benzoyl peroxide in the treatment of mild to moderate papulopustular acne. **Methods:** An observational prospective study was conducted from June 2023 to December 2023 in the dermatology department of Niazi Welfare Foundation Teaching Hospital, Sargodha. 72 patients with mild to moderate papulopustular acne were monitored. A gel containing a combination of 1% clindamycin and 5% benzoyl peroxide was applied once daily for 12 weeks. Descriptive statistics was used for demographic variables. Chi-square test was used to evaluate the treatment effects at a significance level, p-value<0.05. Adverse effects related to therapy were shown as bar chart. **Results:** Findings of the study showed that during therapy in the period between the 3rd and 6th weeks, the proportion of patients who achieved excellent improvement increased by 25% from 40/72 (55.5%) to 57/72 (79.1%) respectively p < 0.05. **Conclusions:** The study concluded that the combination of 1% clindamycin and 5% benzoyl peroxide was effective in treating mild to moderate papulopustular acne.

INTRODUCTION

Acne is a prevalent inflammatory skin condition affecting 9% of the global population [1]. Acne manifest frequently during puberty, between the ages of 12 and 24. The incidence of acne increased among individuals aged 25 to 40 [3, 4]. Acne's impact on quality of life and self-esteem is notably significant, often leading to feelings of depression and anxiety [2, 3]. The pathogenetic links that play a significant role in the development of acne are well known; hypertrophy of the sebaceous glands and excessive formation of sebum, abnormal keratinization of keratinocytes in the area of the mouths of hair follicles, follicular proliferation of *Cutibacterium acnes (C. acnes),* development of inflammation [4, 5]. Modern methods of studying *C. acnes*, based on typing the nucleic acids of microorganisms, have made it possible to establish that this bacterium, which is one of the dominant representatives of the normal microbiome of human skin, consists of phylogenetically different cluster groups [6]. Different phylotypes of *C. acnes* differ significantly in their characteristics, including the ability to initiate inflammation in the skin [7]. If in healthy people *C. acnes* are commensals involved in maintaining the barrier properties of the skin, then in patients with acne other phylotypes of this bacterium act as opportunistic microorganisms and

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are the main triggers of inflammation [8, 9]. In acne, *C. acnes* strains stimulate the production of interleukin-1α by keratinocytes, which leads to their infundibular hyperproliferation and the formation of comedones [10, 11]. A systematic review of scientific articles on the epidemiology of acne revealed that severe cases requiring systemic therapy occur in fewer than 10% of patients for 90% of patients with mild to moderate acne, treatment typically starts with the application of topical medications [12]. Combining pharmacological drug with varying mechanisms of action in a single external dosage form compared with therapy with a single-component agent or sequential use of two topical drugs can provide higher effectiveness and tolerability, reduce antibiotic resistance and increase patient adherence to treatment [13, 14]. Clindamycin belongs to lincosamide antibiotic group and had a bacteriostatic effect against gram-positive aerobic microorganisms as well as a broad spectrum of anaerobic bacteria. Topical clindamycin has proven highly effective in treating papulopustular acne; however, prolonged monotherapy can result in antibiotic resistance in *C. acnes* and lead to disease relapses [15]. Benzoyl peroxide is a highly lipophilic oxidizing agent with bactericidal and mild keratolytic effects. Its nonspecific bactericidal action occurs through the formation of reactive oxygen species that oxidize bacterial proteins. Using benzoyl peroxide helps decrease comedone formation and prevents microorganisms from developing resistance to clindamycin [16].

The current study aimed to assess the effectiveness of a combination drug containing a fixed dose of 1% clindamycin and 5% benzoyl peroxide in treating patients with mild to moderate papulopustular acne.

METHODS

An observational prospective study was carried out from June 2023 to December 2023 in the dermatology department of Niazi Welfare Foundation Teaching Hospital, Sargodha approved by the Institutional Review Board with the letter reference number NM&DC/IRB/407. IRB approval was granted on 1st June 2023. The sample size of 72 patients was calculated based on a 95% confidence level, a 5% margin of error, and the prevalence of acne reported in recent studies in Pakistan [17]. Non-probability convenience sampling was employed. Inclusion criteria involved patients aged over 12 years, with mild to moderate non-papulopustular acne, who were able to adhere to the protocol requirements. Patients with severe papulopustular acne, nodular or conglobate acne, a history of antibiotic-associated colitis, hypersensitivity to clindamycin or lincomycin, pregnancy, breastfeeding, or liver and kidney failure were excluded. Data collection commenced after obtaining the informed consent from participants. Demographic information, including sex, age was collected and, the disease severity assessed according to half-face counting [18]. The subjects were categorized according to following severity scale. Only cases with mild to moderate severity were included: 1) fewer than 10 comedones, 2) between 10 and 25 comedones, 3) between 25 and 50 comedones 4) more than 50 comedones. Before baseline measurements of physiological parameters, it was ensured that the skin area to be measured is clean and free of any cosmetics or lotions. The room was acclimatized to a standard temperature (20-22°C). Sebum on one cheek was determined with Sebummeter SM815 (Courage + Khazaka Electronic GmbH, Germany). The measuring head of the cartridge exposes a 64 mm2 measuring section of an opaque plastic tape which is firmly pressed onto the cheeks for 30s with a slight pressure to collect the sebum. The resulting increase in transparency of the tape was measured and the displayed values correspond to the sebum amount on the face in µg sebum/cm2. Procedure for using the gel was explained to the participants that was to be applied once daily as a thin layer to the area of the rash for period of 3 months. The effect of treatment was assessed at 3rd and 6th week of treatment by examining counts of rashes on half of the face along with measures of physiological parameters. Effectiveness of therapy was based on the reduction in lesions. All the measures were taken at baseline, 3 weeks and 6 week period. Patients were also monitored for adverse events. Main outcome variable of the study was effectiveness of therapy evaluated on scale of acne severity based on percentage of reduction in comedones on half face after 3 weeks of treatment and again after 6 weeks [18]. Statistical data processing was carried out using the software SPSS version 24.0. The normality of distributions was checked using the Shapiro–Wilk test. Descriptive statistics was used for demographic variables. Chi-square test was used to evaluate the treatment effects at a significance level, p-value<0.05. Adverse effects related to therapy were shown as bar chart.

Table 1: Scale of Acne Severity

Scale	Percentage of Reduction	Level
4	100% Reduction	Excellent
3	75–99% Reduction	Good
2	50–74% Reduction	Moderate
1	1–49% Reduction	Insufficient
0	0% Reduction	Unchanged
-1	Increase in Severity	Worse

RESULTS

There were 72 patients, including both men and women aged 14 to 35 years (mean age 20.9 ± 5.7 years), diagnosed with mild to moderate papulopustular acne. Among them, there were 40 men (55.6%, mean age 21.4 ± 4.8 years) and 32 women (44.4%, mean age 19.6 ± 6.5 years). 31 patients (43%) had mild papulopustular acne, while 41 (57%) had

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moderate severity as shown in table 2.

Table 2: Demographics of Study Participant (n=72)

Variables	No. of Participants Range/ (Mean ± SD)/N (%)
Age (Years)	14-35
Mean Age (Years)	20.9 ± 5.7
Gender	
Male	40 (55.6%)
Female	32 (44.4%)
Disease Severity	
Fewer than 10 Comedones	31 (43%)
Between 10 and 25 Comedones	41 (57%)

Table 3 showed that by the end of the 3rd week, over half of the patients had achieved excellent improvement 40 out of 72 (55.5%); improvement was good in 22 out of 72 (30.5%) patients; moderate improvement in 7 out of 72 (10%); and there was insufficient improvement in 3 out of 72 (4.1%) patients. The total proportion of patients who experienced excellent and good improvement was 62 out of 72 (86%). By the end of the 6th week of treatment, 79.1% (57 out of 72) of patients had achieved excellent improvement. The total proportion of patients showing excellent and good improvement was 88.8% (64 out of 72), while insufficient improvement was observed in 2.7% (2 out of 72) of patients. Analysis of the dynamics of the clinical picture showed that during therapy in the period between the 3rd and 6th weeks, the proportion of patients who achieved excellent improvement increased by 25% from 40/72 (55.5%) to 57/72 (79.1%) respectively $p < 0.05$.

Table 3: The Clinical Effectiveness of Therapy

Outcomes	Effectiveness of Therapy N (%)		p-Value
	3 Weeks	6 Weeks	
Excellent	40 (55.6%)	57 (79.1%)	0.01
Good	22 (30.6%)	7 (9.72%)	
Moderate	7 (9.7%)	6 (8.3%)	
Insufficient	3 (4.2%)	2 (2.8%)	
Unchanged	0	0	
Worse	0	0	

During the treatment, some patients experienced side effects such as dry skin (13%, 9 out of 72), redness (20%, 14 out of 72), and a burning sensation after applying the medication (13%, 9 out of 72). These side effects were temporary and resolved without the need for additional prescriptions. No adverse reactions necessitating discontinuation of the medication were reported throughout the study period as shown in figure 1.

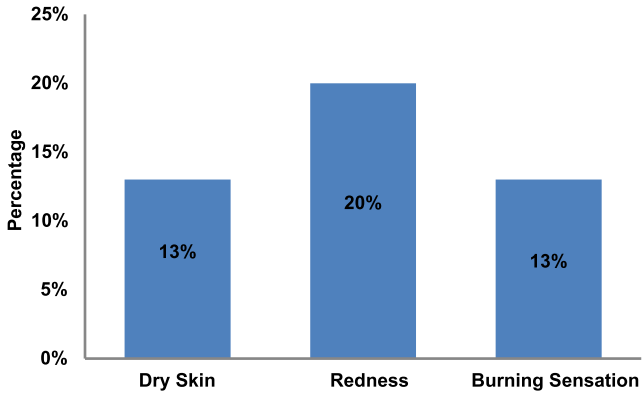

Figure 1: Adverse Effects Reported During the Study

DISCUSSION

This study focuses on evaluating the therapeutic effectiveness and tolerability of a new combination topical medication for acne a gel containing a fixed dose of 1% clindamycin and 5% benzoyl peroxide. The results indicate the high clinical effectiveness. According to findings in table 2, by the end of the 6th week of treatment, 79.1% (57 out of 72) of patients had achieved excellent improvement while it was only 55.5% (40 out of 72) in 3rd week. Another study evaluating the effectiveness of a gel formulation combining benzoyl peroxide and clindamycin demonstrated significantly greater reductions in both inflammatory and total lesions. There were no serious adverse events requiring discontinuation of treatment. The combination gel was generally well tolerated, with only a few patients experiencing short-term adverse events after application of the drug. These findings suggest that the combination therapy is more effective than its individual components [19]. Another study reported that the combination therapy of adapalene and benzoyl peroxide demonstrated a success rate of 89.2%, defined as maintaining the number of inflammatory lesions at ≤10. These findings suggest that the combination treatment regimen is significantly more effective than no treatment in managing inflammatory lesions [20]. Similarly, Mohsin N *et al.*, in 2022 study also indicated the significant effectiveness of combination therapy using benzoyl peroxide and clindamycin for acne treatment, as it offers superior effectiveness in improving acne and reducing both inflammatory and total lesions [21]. The combination of 1% clindamycin and 5% benzoyl peroxide proved significant in improving acne, with notable results in 6 weeks therapy. However, as an observational study, emphasizing the need for experimental studies with controls to investigate the effectiveness of combination regimen further. Future clinical trials are needed to evaluate the effectiveness of dual therapies for more definite results.

CONCLUSIONS

The study concluded that the combination of 1% clindamycin and 5% benzoyl peroxide was effective in treating mild to moderate papulopustular acne.

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Combination regime proved effective and well tolerated than individual ingredient alone.

Authors Contribution

Conceptualization: SN
Methodology: SN, SM, ZP
Formal analysis: AG
Writing, review and editing: MAH, SA, ZP

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Postoperative Outcomes and Surgical Complications in Typhoid Ileal Perforation

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ABSTRACT

Surgical repair for typhoid ileal perforation is essential to prevent peritonitis and sepsis. Postoperative outcomes, which include survival rates and recovery times, underscore the importance of comprehending surgical complications to refine treatment strategies and enhance patient survival. **Objective:** To determine postoperative outcomes and surgical complications in typhoid ileal perforation. **Methods:** The prospective cohort was conducted at General Surgery Department of Liaquat University Hospital in Hyderabad & Jamshoro. 228 Patients of age 18 years or more and of any gender, who were operated for having single typhoid ileal perforation, were included in the study. While patients with multiple perforations, TB peritonitis or having traumatic perforations, were excluded from the study. **Results:** The most common age group was found to be 18-30 years (40.4%), followed by 31-40 years (28.1%), 41-50 years (19.3%), 51-60 years (7.9%), and >60 years (4.4%). Males comprised 57.9% of the population, while females made up 42.1%. The mean length of hospitalization was found to be 14 ± 5 days. The majority of patients experienced good outcomes, accounting for 158 individuals (69.3%), while 70 patients (30.7%) had adverse outcomes. Among the adverse outcomes, there was a mortality rate of 7.2% (16 patients) and 54 patients (23.7%) experienced complications, some experienced more than one complication. **Conclusions:** The study concluded that though the majority of patients recover well, a significant proportion (7.2%) still faced adverse postoperative outcomes in terms of mortality. 54 patients (23.7%) experienced complications, some experienced more than one complication.

INTRODUCTION

Typhoid Ileal Perforation (TIP) is a significant complication of typhoid fever, especially in developing countries. It requires urgent surgical intervention and is a daunting task for surgeons, especially in resource limited region [1]. The high morbidity and mortality related to TIP have been mostly related to postoperatory complications, persistent peritonitis and septicemia [2, 3]. Historically, typhoid fever caused by *Salmonella enterica serovar typhi* has been a major global public health problem, with 11 to 21 million cases and 128,000 to 161,000 deaths reported annually [1-3]. The frequency of TIP hospitalizations shows wide variation from place to place, reflecting differences in healthcare. Typhoid fever is highly endemic in South Asia with an annual incidence rate of about 493 cases per 100,000 people in Pakistan, for example [6, 7]. Surgical treatment for TIP includes the following procedures, such as; primary repair, resection with anastomosis and stoma formation. The decision for surgical approach depends upon both the general status of the patient, the size of the perforation and any other concomitant morbidity e.g. peritonitis. For early presenting patients with minimal contamination, primary repair with suturing of the perforation is the general method of choice [8]. In more severe cases of typhoid ileal perforation involving large perforations, extensive fecal contamination and delayed presentation, surgical management may necessitate resection with anastomosis or stoma formation. The prone position is optimal for these procedures due to its unique advantages and risks, which are anticipated to impact recovery and the incidence of complications significantly

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[9]. Postoperative outcomes in TIP patients are majorly determined based on type of surgery done as well as its corresponding complications. The research suggests that primary repair has significantly less postoperative complications and reduced hospital stay compared with resection with anastomosis or creation of an stoma [10]. However, there is a risk of perforation recurrence and postoperative peritonitis [10]. Closure of perforations and outlet resections are employed for abscess drainage and wound patching, albeit with higher complication rates. Stoma creation with anastomosis is preferred for severe perforations, but both options are associated with increased complication rates and prolonged hospitalization. Therefore, the surgical approach's biomechanical invasiveness plays a crucial role in long-term functional recovery and pain management following TIP treatment [11]. Complications that can occur post TIP differ and contain wound infections, intra-abdominal abscesses, enterocutaneous fistulas and respiratory problems. The most common complication are wound infection and intra-abdominal abscess developing ones can derail recovery [12, 13]. Even with advances in surgical techniques, TIP still causes significant illness and death, especially in developing countries, due to the high rate of postoperative complications.

This study was aimed to determine postoperative outcomes and surgical complications in typhoid ileal perforation to improve patient management and outcomes.

METHODS

The prospective cohort was conducted at General Surgery Department of Liaquat University Hospital in Hyderabad & Jamshoro. Patients of age 18 years or more and of any gender, who were operated for having single typhoid ileal perforation, were included in the study, via consecutive sampling technique, from January 2022 to December 2022. While patients with multiple perforations, TB peritonitis or having traumatic perforations, were excluded from the study. All the patients were briefed about the research process and informed written consent was taken prior to enrollment in the study. Openepi sample size calculator was used to calculate sample size of 228 patients by taking prevalence of thyroid related perforations as 30% and a margin of error of 5% and a confidence level of 90% [14]. The study was approved by Institutional ERC vide letter no. LUMHS/REC/-84, dated; 03/05/2021. Postoperative outcomes were measured in terms of length of hospitalization, mortality and post-surgical complications. Patients with no post-surgical complications and successful recover were labelled as having good outcome. While patients encountering mortality, wound infections, wound insufficiency, pneumonia, intestinal obstruction, abdominal wound dehiscence, enterocutaneous fistula, incisional hernia, and empyema of the pleural cavity were labelled as having adverse outcomes. Daily follow up were done as part of hospital protocol during the course of hospitalization while weekly follow up was done after discharge. Postoperative outcomes were assessed till 30th day. Wound insufficiency was defined as the failure of a surgical wound to heal properly, often marked by delayed or incomplete closure, leading to persistent drainage, infection, or wound edge breakdown while abdominal wound dehiscence was defined as partial or complete separation of the layers of a surgical wound, typically along the suture or staple line, after closure. The primary surgical interventions involved primary closure, resection with anastomosis, and stoma formation. Primary closure involves directly suturing the perforation site, often suitable for smaller perforations with minimal contamination. Resection with anastomosis entails removing the affected segment of the ileum and reconnecting the healthy ends of the intestine, which was preferred for larger perforations or cases with significant fecal contamination. Stoma formation, either temporary or permanent, was made to divert intestinal contents away from the site of the perforation to allow healing. The choice of technique depended on the size and location of the perforation, the presence of contamination, and the overall clinical condition of the patient. During all surgeries, the peritoneal cavity was thoroughly irrigated with a large volume of normal saline solution. Peritoneal drainage was utilized in 218 cases. All abdominal wall incisions, including those on the skin, were sutured closed. Postoperatively, all patients were managed as per hospital protocols. Data analysis was performed using SPSS version 24.0.

RESULTS

The most common age group was found to be 18-30 years (40.4%), followed by 31-40 years (28.1%), 41-50 years (19.3%), 51-60 years (7.9%), and >60 years (4.4%). Males comprised 57.9% of the population, while females made up 42.1%. The BMI distribution showed that 62.3% had a normal BMI (18.5-24.9 kg/m^2), 14.9% were underweight (<18.5), 16.7% were overweight (25-29.9), and 6.1% were obese (≥30) (Table 1).

Table 1: Descriptive Statistics

Variables	Statistics N (%)
Age Distribution (Years)	
18-30	92 (40.4%)
31-40	64 (28.1%)
41-50	44 (19.3%)
51-60	18 (7.9%)
>60	10 (4.4%)
Gender	
Male	132 (57.9%)
Female	96 (42.1%)

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BMI (Kg/m^2)	
<18.5	34 (14.9%)
18.5-24.9	142 (62.3%)
25-29.9	38 (16.7%)
≥30	14 (6.1%)

The mean length of hospitalization was found to be 14 ± 5 days. The majority of patients experienced good outcomes, accounting for 158 individuals (69.3%), while 70 patients (30.7%) had adverse outcomes. Among the adverse outcomes, there was a mortality rate of 7.2% (16 patients), and 54 patients (23.7%) experienced complications (Table 2).

Table 2: Postoperative Parameters and Adverse Outcomes in Typhoid Ileal Perforation

Variables	Frequency (%)/Mean ± SD
Mean Length of Hospitalization (days)	14 ± 5
Good Outcomes	158 (69.3%)
Adverse Outcomes	70 (30.7%)
Adverse Outcomes	
Mortality	16 (7.2%)
Patients with Complications	54 (23.7%)

In total, 54 patients (23.7%) experienced complications, some experienced more than one complication. The most common complication was wound infection, occurring in 24 patients (10.5%), followed by pneumonia in 18 patients (7.9%) and wound insufficiency in 14 patients (6.1%). Other complications included incisional hernia in 12 patients (5.3%), intestinal obstruction in 10 patients (4.4%), and abdominal wound dehiscence in 8 patients (3.5%). Less frequent complications were enterocutaneous fistula in 6 patients (2.6%) and empyema of the pleural cavity in 4 patients (1.8%) (Table 3).

Table 3: Postsurgical Complications In Typhoid Ileal Perforation

Complications	Frequency (%)
Wound Infection	24 (10.5%)
Wound Insufficiency	14 (6.1%)
Pneumonia	18 (7.9%)
Intestinal Obstruction	10 (4.4%)
Abdominal Wound Dehiscence	8 (3.5%)
Enterocutaneous Fistula	6 (2.6%)
Incisional Hernia	12 (5.3%)
Empyema of the Pleural Cavity	4 (1.8%)
Total Patients with Complications	54 (23.7%)

DISCUSSION

Mortality rates associated with typhoid perforation remain significantly high, ranging from 20% to over 50% with surgical intervention and exceeding 40% with conservative management [1, 14, 15]. Contributing factors to these elevated mortality rates include persistent postoperative peritonitis, septicemia, and anemia along with early mechanical intestinal obstruction, and enterocutaneous fistulae exacerbate patient outcomes and pose challenges for surgical management, further elevating mortality risks. Preoperatively, these patients often present in a debilitated, dehydrated, and anemic state [16]. In our study, the most prevalent postoperative complication was wound infection, observed in 10.5% of patients, corroborating previous findings that identify wound infection as a common postoperative issue [17]. Other significant complications included pneumonia (7.9%), wound insufficiency (6.1%), and incisional hernia (5.3%). Although suture failure is linked to high mortality rates, it was less common in our population [14]. These findings may reflect advancements in surgical techniques and patient management protocols. Our study's overall morbidity rate was 23.7%, which, though still substantial, is considerably lower than the previously reported rates exceeding 70% [18]. This reduction may be attributed to improved postoperative care, timely medical interventions, and a comprehensive antibiotic regimen. The mortality rate in our study was 7.2%, markedly lower than historical averages, indicating enhanced management of patients with typhoid ileal perforation [19]. In the early surgical intervention for Typhoid Ileal Perforation (TIP), it is crucial to select a procedure that allows rapid and easy access to the inner abdomen. This facilitates the identification and two-layer closure of all perforations, a technique employed in 99.1% of our patients [20]. Postoperative intestinal fistulae are significant contributors to morbidity and mortality among patients who survive the septicemic phase of typhoid perforation [21].In this study, six patients developed postoperative enterocutaneous fistulae; all were managed conservatively and had an average hospital stay of 14 ± 5. Four of these fistulae closed spontaneously, while two cases resulted in fatalities. Each complication was addressed promptly and appropriately. Infected wounds were treated with suitable antibiotics following wound culture results. The majority of insufficient wounds (85%) were secondarily sutured once clean; the remainder healed by secondary intention. Patients who developed early postoperative mechanical intestinal obstruction had a second surgery (relaparotomy) and removal of adhesions right after the diagnosis was confirmed. Abdominal wound openings (dehiscences) that occurred within 5-7 days after the initial surgery were treated as emergencies. They were re-sutured immediately as per hospital protocol. The 4 (1.8%) patients with empyema were successfully treated with cest tube and passive drainage. Our study identified persistent postoperative peritonitis, septicemia, and anemia as primary contributors to mortality in TIP cases [16]. Despite a mortality rate of 7.2% in our series lower than previously reported ranges postoperative complications continue to extend hospital stays and increase patient suffering [1, 19]. The overall morbidity rate of 23.7% in our study underscores the need for ongoing refinement of surgical techniques and postoperative care

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protocols to improve outcomes for TIP patients. The result from this series illustrate the challenges TIP presents to general surgeons. Prompt surgical intervention is essential, but the potential for multiple postoperative complications necessitates preparedness to manage these issues promptly to reduce morbidity and mortality.

CONCLUSIONS

The study concluded that though the majority of patients recover well, a significant proportion (7.2%) still faced adverse postoperative outcomes in terms of mortality. 54 patients (23.7%) experienced complications, some experienced more than one complication. The most common complications were wound infection, followed by pneumonia and wound insufficiency.

Authors Contribution

Conceptualization: IRK
Methodology: IRK, AR, KA, MBR, ZA
Formal analysis: IRK
Writing, review and editing: SNK, AR, KA, MBR, ZA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Robson Criteria to Determine the Risk of Cesarean Section in Females Presenting to Sir Ganga Ram Hospital (SGRH), Lahore

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ABSTRACT

Rates of caesareans have increased, resulted in unfavourable outcomes in subsequent pregnancies. Robson categorization enhances standard of care by optimising the use of C-sections and evaluating methods to lower caesarean rates. **Objective:** To determine the frequency of caesarean section and to determine frequency of Robson 10 group classification system in patients who undergo caesarean. **Methods:** In this cross-sectional study, 140 pregnant selected via simple random sampling, were enlisted from Gyne department of SGRH, Lahore. According to Robson 10-group categorization those who underwent C-section were divided into ten groups and indication of C-section was studied. Data scrutiny was done using SPSS version 26.0. Mean and SD was used for quantitative variables and frequency for qualitative data. Data were stratified for effect modifiers, p-≤0.05 was taken as significant. **Results:** Mean age of patients calculated was 31.94 ± 2.14 years. Out of 140, 23.6% had C-section and 76.4% had vaginal delivery. According to class of modified Robson criteria, 12.1% had class 1, 12.1% had class, 2, 21.2% had class 3, 36.4% had class 5, and 3.0% each had class 4, 6, 7, 8, 9, and 10. **Conclusions:** According to our findings, considerable percentage of C-sections occur with previous C-sections serving as most common indicator. This pattern emphasizes how crucial it is to concentrate on primary preventive techniques in order to lower its rate. Large number of C-sections performed on nulliparous both those in spontaneous labour and those who were not indicates that labour management procedures and decision-making processes need to be closely examined.

INTRODUCTION

Caesarean section, can save patient's life when difficulties during pregnancy or labour emerges. It is major surgery with direct vulnerability to both mother and fetus, despite its vital significance in some cases. In addition, there may be long-term consequences from C-sections that are currently being studied, as well as complications for subsequent pregnancies [1, 2]. The number of caesareans performed worldwide is on rise, especially in growing Asian countries. This increase is happening despite lack of data indicating that higher rates of caesarean sections offer significant benefits for mothers and newborns [3]. Because of this steady rise, lack of agreement over ideal rate for caesareans, short and long-term dangers and expenses involved, caesarean rates continue to raise concerns worldwide [2]. WHO reports that caesarean proportions have been rising in both industrialized and

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underdeveloped nations? According to WHO, rate for caesareans should be between 10-15%. % [4]. In Pakistan, frequency of unnecessary C-sections has been doubled during last 20 years [4, 5]. In 1985, WHO stated that more than 10-15% of caesareans performed lacked medical rationale? While the number of caesareans executed globally has increased significantly over the next three decades, questions have been raised about accuracy of this historic 1985 remark [6]. So, WHO advises using Ten-Group Robson classification as international strategy for evaluating caesarean procedures in order to enable meaningful comparisons [7-9]. Ten-Group Classification was proposed by Robson to permit dire inquiry agreeing to individualities. Features are: (i) solo or multiple pregnancy, (ii) nulliparous/multiparous/multiparous with former cesarean, (iii) cephalic, breech/other mal-presentation, (iv) unplanned/induced labor, and (v) term/preterm. On foundation of these variables, there are divisions of females in 10 groups [8, 10]. In one study done on pregnant who underwent C-section, frequency of cesarean noted was 30% for primigravidas and 70% for multigravidas [11]. In another study done, 20.3% females underwent cesarean. According to Robson, class 1 found was 13%, 8.1% class 2, 2.6% in class 3, 61% class 4, and 58.2% class 5 [12]. Another study found that rate of females who fell in class 1 was 12.8%, in class 2 was 18.1%, in class 3 was 26.5%, in class 4 was 2.1%, in class 5 was 27.7%, in class 6 was 0.33%, in class 7 was 0.35%, in class 8 was 1.6%, in class 9 was 2.2% and in class 10 was 5.9%. Maximum contribution 27.42% to total cesarean section rate was made by Group 5 and 7.34% by Group 2. These three groups contributed 87% towards total cesarean section rate. Small Groups 6, 7, 8, 9, and 10 had high cesarean section rates but small overall contribution [13]. Rationale of this study is to determine frequency of cesarean delivery and frequency of cesarean delivery in females obtain particular score of modified Robson criteria. Through literature, it has been noticed mostly females fell in classes 5-9. So this classification can help to determine the mode of delivery of fetus and can help to preserve labor time and plan appropriate mode of delivery instead of waiting for labor or complications. But, not much work has been done in this regard. So, there is a need to conduct this study to get local data and implement results of this study in local setting and can improve our practice. Objective of this study is to determine the frequency of cesarean presenting at term and to determine the frequency of Robson 10 group classification system in patients who undergo cesarean.

METHODS

This cross sectional study, was conducted at department of Obstetrics and Gynecology, SGRH, Lahore from 30-07-2022 to 30-01-2023 after taking ethical approval from IRB and acceptance of proposal from CPSP/REU/OBG-2019-059-9373. 140 females were estimated by keeping confidence level 95%, margin of error 7% and expected prevalence of cesarean section as 23.5% [14]. Written informed consent was taken from all patients. Patients aged 18 to 40 years, primigravidas and multigravida (upto 3), having gestational age >37 weeks on LMP and on regular antenatal checkup were included. Those with congenital fetal abnormalities, placenta previa/increta/accrete/percreta/ abruption (detected on ultrasound), pregnancy induced hypertension (BP≥140/90mmHg), gestational diabetes (BSR>200 mg/dl), Cephalic pelvic disproportion, previous more than 2 c/section and grand multipara (>3) were excluded. After taking consent their demographic summary i.e. age, gestational age, parit and BMI noted on given proforma. All females were delivered either by cesarean sections or normal vagina delivery. Then females who underwent C-section were evaluated for modified Robson criteria and divided in 10 groups according to classification (table 1). Females were followed till delivery. Females undergoing cesarean, were classified for Robson 10 group classification system. Data were collected using questionnaire comprises two sections: 1) Section one acquired information on sociodemographic variables such as age, parity, BMI, mode of delivery etc. 2) Section two collects data based on the Robson classification system as shown in table 1. SPSS version 26.0 was used to enter to analyze the collected data. Mean and SD were computed for age, gestational age and BMI. Frequency and percentage was computed for cesarean section, parity and Robson class. Chi-square test was applied to compare the frequency of cesarean section among data stratified for age, gestational age, parity and BMI. Post-stratification, Chi-square test was applied. P-value≤0.05 was taken as significant. Out of 69 primigravidas 49 (71.0%) had C-sections. In table 1, distribution of patients undergoing caesarean section according to the Robson 10 Group Classification System elaborated.

Table 1: Robson 10 Group Classification System

Groups	Clinical characteristics
1	Nulliparous, singleton, cephalic, ≥ 37 weeks, spontaneous labor
2	Nulliparous, singleton, cephalic, ≥ 37 weeks, induced labor or cesarean section before labor
3	Multiparous without previous cesarean section, singleton, cephalic, ≥ 37 weeks, spontaneous labor
4	Multiparous without previous cesarean section, singleton, cephalic, ≥ 37 weeks, induced labor or caesarean section before labor
5	Multiparous without prior cesarean section, singleton, cephalic, ≥ 37 weeks
6	All nulliparous breeches
7	All multiparous breeches (including previous cesarean section)
8	All multiple pregnancies (including previous cesarean section)

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9	All pregnancies with transverse or oblique lie (including those previous cesarean section)
10	Singleton, cephalic, ≤36 weeks (including previous cesarean section)

RESULTS

Table 2 showed demographic characteristics of our study population in terms of mean ± SD. Mean age calculated was 31.94 ± 2.14 years, gestational age 39.69 ± 1.14 weeks and mean of BMI noted was 27.77 ± 5.91 kg/m^2.

Table 2: Sociodemographic Characteristics of the Participants Presented with Mean and Standard Deviation (n=140)

Variables	(Mean ± SD)
Age (Years)	31.94 ± 2.14
BMI (Kg/m^2)	27.77 ± 5.91
Gestational Age (Weeks)	39.69 ± 1.14

Table 3 showed qualitative variables in terms of frequency and %, parity distribution of patients was done, it showed that 49.3 % (n=69) were primigravidas whereas 50.7% (n=71) were multigravida. Frequency of age distribution has shown that out of 140 patients, 21.4 % (n=30) were in age group of 18-30 years and 78.6 % (n=110) were in age group of 31-40 years. Total of 140 females, 23.6% (n=33) had cesarean section and 76.4% (n=107) had normal vaginal delivery.

Table 3: Characteristics of the Participants Presented with Frequency and Percentages

Variables	N (%)
Age	
18-30 Years	30 (21.4%)
31-40 Years	110 (78.6%)
Total	140 (100%)
Parity	
Primigravida	69 (49.3%)
Multigravida	71 (50.7%)
Total	140 (100%)
Mode of Delivery	
Cesarean Section	33 (23.6%)
Normal Vaginal Delivery	107 (76.4%)
Total	140 (100%)

As shown in table 4, According to class of modified Robson criteria on 33 patients who underwent C-section, 12.1% (n=4) had class 1, 12.1% (n=4) had class, 2, 21.2% (n=7) had class 3, 3.0% (n=1) had class 4, 36.4% (n=12) had class 5, 3.0% (n=1) had class 6, 3.0% (n=1) had class 7, 3.0% had (n=1) class 7, 3.0% (n=1) had class 8, 3.0% (n=1) had class 9, and 3.0% (n=1) had class 10.

Table 4: Frequency Distribution of Modified ROBSON Criteria among Patients having C-section

Class of Modified Robson Criteria	N (%)
Nulliparous, Single Cephalic, >37 Weeks in Spontaneous Labor	4 (12.1%)
Nulliparous, Single Cephalic, >37 Weeks, Induced Or Cs Before Labor	4 (12.1%)
Multiparous (Excluding Previous CS), Single Cephalic, >37 Weeks in Spontaneous Labor	7 (21.2%)
Multiparous (Excluding Previous CS), Single Cephalic, >37 Weeks, Induced or CS Before Labor	1 (3.0%)
Previous CS, Single Cephalic, >37 Weeks	12 (36.4%)
All Nulliparous Breeches	1 (3.0%)
All Multiparous Breeches (Including Previous CS)	1 (3.0%)
All Multiple Pregnancies (Including Previous CS)	1 (3.0%)
All Abnormal Lies (Including Previous CS)	1 (3.0%)
All Single Cephalic, <36 Weeks (Including Previous CS)	1 (3.0%)
Total	33 (100.0%)

Data stratification with respect to age, BMI, gestational age and parity remained statistically not significant p >0.05, as shown in table 5. Data stratification of parity has shown that among primigravidas out of 69, 20 (29.0%) had C-section and 49 (71.0%) had vaginal delivery and among multigravidas out of 71, 13 (18.3%) had C-section and 58 (81.7%) had vaginal delivery, p=0.137, statistically not significant. For BMI 17-25 Kg/m^2 out of 37 patients 9 (24.3%) had C-section and 28 (75.7%) had vaginal delivery, for BMI >25 Kg/m^2 out of 103 patients 24 (23.3%) had C-section and 79 (76.7%) had vaginal delivery, p=0.900 not significant statistically. For >37-40 weeks out of 100 patients 25 (25.0%) had cesarean mode of delivery, while 75 (75.0%) had vaginal delivery and for >40 weeks, out of 40 patients 8 (20.0%) had C-section while 32 (80%) had vaginal delivery, p=0.529. For age group 18-30 years, out of 30 patients 8 (26.7%) had C-section, while 22 (73.3%) had vaginal delivery, and for 31-40 years out of 110 patients 25 (22.7%) had C-section and 85 (77.3%) had vaginal delivery, p=0.652 this difference was not significant statistically.

Table 5: Data Stratification

Variables		Mode of Delivery N (%)		Total	p Value
		Cesarean Section	Normal Vaginal Delivery		
Parity	Primigravida	20 (29.0%)	49 (71.0%)	69	0.137
	Multigravida	13 (18.3%)	58 (81.7%)	71	
	Total	33 (23.6%)	107 (76.4%)	140	
BMI Group	17-25 Kg/m^2	9 (24.3%)	28 (75.7%)	37	0.900
	>25 Kg/m^2	24 (23.3%)	79 (76.7%)	103	
	Total	33 (23.6%)	107 (76.4%)	140	
Gestational Age Group	>37-40 Weeks	25 (25.0%)	75 (75.0%)	100	0.529
	>40 Weeks	8 (20.0%)	32 (80.0%)	40	
	Total	33 (23.6%)	107 (76.4%)	140	
Age Group	18-30 Years	8 (26.7%)	22 (73.3%)	30	0.652
	31-40 Years	25 (22.7%)	85 (77.3%)	110	
	Total	33 (23.6%)	107 (76.4%)	140	

DISCUSSION

Our study shows that out of 140 patients, 21.4 % (n=30) were in age group of 18-30 years and 78.6 % (n=110) were in age group of 31-40 years. Mean age was calculated as 31.94 ± 2.14 years. Distribution of gestational age was 39.69 ± 1.14 weeks and BMI was 27.77 ± 5.91 kg/m2. Parity stratifications of patients shows that 49.3 % (n=69) were primigravidas

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whereas 50.7% (n=71) were multigravida. Out of Total of 140 females, 23.6% (n=33) had cesarean section delivery and 76.4% (n=107) had normal vaginal delivery. In one preceding study, caesarean section rate noted was 48.28% which is quite high paralleled to WHO criteria (15%) [15]. One study conducted has shown frequency of caesarean sections 46.93% slightly high from our frequency noted, and similar to our results among them Group 5 had greatest rate of caesareans (39.60%) and Group 2 had 18.21% [16]. Similarly, study from 2016-2017 in, Nepal, on 3,817 women and were investigated by means of this classification. Women with previous CS (Group 5) encompass main proportion (9.4%) of total 26.41% CS rate. In India, one study found that there was trend of amplified fraction of cesarean in group and 2 which was 36% and 36.71% respectively [17]. Likewise, in India 2004 to 2013, cesarean rate was 25.17 %. Major influences to this were found to be group 1 (37.62 %) [18, 19]. Based on proportion of live births in each of Robson's categories and proportion of C-sections for every group, one study has examined the pregnancies in which 2, 764, 373 pregnant women had C-sections yielding 51.9% overall C-section rate. R5 group's C-section rate rose gradually from 22.2% in 2013 to 24.3% in 2016. This pattern is explained by the fact that C-sections performed in R1-4 group's cause these women to become pregnant again, which forces them to undergo C-sections [20]. Overall caesarean section CS rate found in one recent study was 35.08%, almost similar to our observation and among them largest group was Group 1 (35.69%), followed by Group 3 25.75% and Groups 1 and 2 had lower CS rates compared to other groups, but these rates were still higher than WHO implementation guidelines. In the analyzed sample study population, the CS rate due to fetal distress was 28.54%, and rate due to previous CS was 25.85% [21]. Missing data can distort the estimate of intended result and reduce representativeness of sample. Convenience sample could create selection bias. We are unable to generalise the results to target population since subgroups in sample are underrepresented in population of interest. The current study's cross-sectional methodology and small sample size limit the quantity of data that can be gathered at any given time. Future clinical practice should focus on developing standardized guidelines and enhancing training for healthcare providers to ensure the appropriate use of caesarean sections.

CONCLUSIONS

According to our findings, Robson categorization system may be used to analyze, screen, audit, and compare caesarean rates. It can also be used to develop and implement efficient plans aimed at achieving WHO-recommended C-section rates.

Authors Contribution

Conceptualization: SH, HMZ, SK[1]
Methodology: AN
Formal analysis: SK[1]
Writing, review and editing: HMZ, AN, MF, BJ, AY, SK[1], SA, Sk[2]

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Maternal Obesity as a Risk Factor for Preterm Delivery in Dichorionic Twin Pregnancies

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ABSTRACT

The prevalence of maternal obesity has been steadily rising in recent decades, posing a significant global health concern particularly in the field of obstetrics. **Objective:** To assess the association between maternal obesity and preterm birth in dichorionic twin pregnancies. **Methods:** This descriptive study was carried at Department of Obstetrics and Gynecology, Khyber Teaching Hospital, Peshawar during the period 1st January 2020 till 31st December 2021. The study included 122 pregnant women in the age range 18 to 45 years diagnosed as dichorionic twin pregnancy presenting with labor. Gestational age at the time of delivery was calculated to record preterm delivery. Pre-pregnancy BMI was retrieved from medical record taking BMI ≥30.0kg/m2 as cut off for obesity. Data were analyzed using SPSS version 25.0. **Results:** The mean age was 31.2 years with 49.2% (n=60) fell into the age range of 30-39 years. 52.5% (n=64) of the participants were nulliparous. 42.2% patients (n=52) had a bad previous obstetrics history. Maternal obesity was observed in 49.2% patients (n=60). The spearman r value for preterm delivery and BMI was 0.710. **Conclusions:** Significant proportion of women with dichorionic twins and preterm delivery were found obese. The risk of preterm delivery in dichorionic twins increases with maternal obesity.

INTRODUCTION

The prevalence of maternal obesity has been steadily rising in recent decades, posing a significant issue in the field of global health [1]. In 2016, the World Health Organization (WHO) reported that over 40% of adults (aged 18 and older) were classified as overweight, while an additional 13% were categorized as obese. The prevalence of maternal obesity prior to becoming pregnant has been reported in 29.0% women in USA, 26.8% to 54% in Europe, 27.3% in India and 36.7% in Pakistan [2, 3]. Obesity during pregnancy has an impact on both the maternal and fetal well-being [4]. Maternal obesity has implications both in terms of maternal and fetal health such as preterm delivery [5, 6]. Preterm delivery refers to the birth of the baby prior to attaining the normal gestational age of 37 weeks. Preterm delivery is a high risk pregnancy and carries high neonatal morbidity and mortality [7, 8]. The deleterious effects of preterm delivery are not limited to immediate or early complications but also extends to long term effects in case of survival of the baby carrying posing sociofinancial issues [9]. The gravity of preterm delivery increases further while dealing with multiple pregnancies such as dichorionic twins from clinical point of view, dichorionic pregnancy is an altogether separate entity which intricate physiological and clinical challenges as compared to singleton pregnancy [10]. The implications of maternal obesity with preterm delivery in the scenario of dichorionic twins have been seldomly studied. Though previous studies have illustrated association between maternal obesity and preterm delivery in case of singleton pregnancy, the understanding about dichorionic twins is scarce [12]. It is

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vital to obtain insights about the clinical and socio-financial implications of maternal obesity on the outcomes of dichorionic pregnancy, particularly the gestational age at the time of delivery. This study aimed to assess the association between maternal obesity and preterm delivery in dichorionic pregnancies. Results of this study will help in better counselling of such patients. It will enable obstetrician in early identification of high risk pregnancy, which will be make the alert to comprehend and timely application of targeted intervention.

METHODS

This is a prospective descriptive study, carried out at department of Obstetrics and Gynecology, Khyber Teaching Hospital, Peshawar, during the period 1st January 2020 till 31st December 2021. Approval for the conduct of the study was granted vide no: 10/DME/KMC, dated 21-12-2019. The study enrolled 122 pregnant women in the age range 18 to 45 years with dichorionic twin pregnancies presenting in labour. Patients with unavailable pre-pregnancy BMI record, prior history of cesarean section, patients with intrauterine death and patients with fetal anomalies were excluded. Dichorionic twins were confirmed on ultrasound. Labor was confirmed clinically with cervical dilatation more 5 cm or above and uterine contraction effective enough for progressive enhancement and effacement. Preterm delivery was defined by the birth of the baby prior to 37 weeks of gestation. Sample size was calculated using WHO sample size calculator taking anticipated proportion of preterm delivery in twin pregnancy was 10.6% with 5% margin of error and 95% confidence interval [12]. Non probability convenient sampling technique was used to enroll participants. We used documented medical records to gather data on the mother's demographic characteristics, medical and obstetrical background, pre-pregnancy Body Mass Index (BMI) and ante-natal care. BMI was calculated using the formula weight in kilograms divide by height in meter squared. BMI was graded as normal (18.5-24.9kg/m^2), overweight (25.0-29.9kg/m^2) and obese (≥30.0kg/m^2). Gestational age was calculated as per last menstrual period. Preterm delivery was confirmed by the delivery of the baby prior to 37 weeks of gestation. Deliveries were carried out in the labor room of the hospital. All deliveries were managed as per hospital protocol for high risk pregnancy. Cesarean section was performed in case of failure of labor to progress or risk of fetal demise. Pregnancy outcomes were noted. Data entry and analysis was carried out using statistical analysis program IBM SPSS version 25.0. Descriptive statistics were used to summarize the characteristics of the study population. Means and standard deviations were recorded for quantitative variables like age, gestational age, and maternal BMI while frequencies and percentages were computed for qualitative variables like parity, diabetes, hypertension and preterm delivery. BMI was calculated using the formula BMI = weight in kilograms/height in meter2). Preterm delivery was stratified by age, parity, obstetrical history and medical history to control the effect modifiers. Post stratification chi square test was applied at 5% level of significance. The association between maternal obesity and pre-term delivery was measured using chi square test. The strength of association was analyzed using Spearman correlation coefficient r value. P value ≤0.05 was considered statistically significant.

RESULTS

Out of the 122 pregnant women the mean age was 31.2 ± 5.96 years. 49.2% (n=60) fell into the age range of 30-39 years, while 34.4% (n=42) were in the age group of 20-29 years. 52.5% (n=64) of the participants were nulliparous, while 47.5% (n=58) were multiparous as shown in table 1.

Table 1: Maternal Demographics of Study Participants (n = 122)

Demographics And Baseline Variables	Frequency (%)
Maternal Age (Years)	
<20 Years	8 (6.6%)
20-29 Years	42 (34.4%)
30-39 Years	60 (49.2%)
≥40 Years	12 (9.8%)
Parity	
Nulliparous	64 (52.5%)
Multiparous	58 (47.5%)

Of the individuals who shared details about their obstetric history, 57.4% (n=70) reported no complications in a previous pregnancy, whereas 42.6% (n=52) had complications like ante-partum or post-partum hemorrhage, ectopic pregnancy, pre-eclampsia and eclampsia in a previous pregnancy. The most prevalent pre-existing medical issues among participants were hypertension (n=20, 16.4%), diabetes (n=10, 8.2%), and other medical disorders (n=6, 4.9%) as reported in table 2.

Table 2: Maternal Characteristics and Medical History (n = 122)

Variables	Frequency (%)
Obstetric History (PPH, Preeclampsia, Eclampsia, Ectopic Pregnancy)	
No Previous Complications	70 (57.4%)
Previous Complications	52 (42.6%)
Pre-existing Medical Conditions	
None	86 (70.5%)
Hypertension	20 (16.4%)
Diabetes	10 (8.2%)
Other	6 (4.9%)

As illustrated in table 3, the proportion of patients with respect to BMI was; underweight 4.9% (n=6), normal weight was 24.6% (n=30), overweight was 21.3% (n=26) and obesity was 49.2% (n=60).

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Table 3: Pre-pregnancy BMI Distribution (n = 122)

Pre-Pregnancy BMI Category	Frequency (%)
Normal Weight (18.5–24.9 kg/m^2)	36 (29.5%)
Overweight (25.0–29.9 kg/m^2)	26 (21.3%)
Obesity (≥30.0 kg/m^2)	60 (49.2%)

Out of the total babies delivered, 72.1% (n=172) of the neonates were delivered at term, whereas 27.9% (n=68) were born preterm. The mean gestational age was 35.5 weeks. Approximately 71% (n=174) of newborns weighed 2,500 grams or more at birth, whereas 23% (n=56) fell between the weight range of 1,500 to 2,499 grams. After 5 minutes, 92.6% (n=226) of the babies had Apgar scores of 7 or above. For Preterm Delivery (<37 Weeks) n= 122, for Birth Weight (Grams) n= 244 and for Apgar Score at 5 minutes n= 244, as illustrated in table 4.

Table 4: Maternal and Neonatal Outcomes (n = 610)

Neonatal Outcomes	Frequency (%) / mean ± SD
Gestational Age (Weeks)	35.5 ± 1.7
Preterm Delivery (<37 Weeks)	
Yes	34 (27.9%)
No	88 (72.1%)
Birth Weight (Grams)	
<1500 Grams	14 (5.7%)
1500-2499 Grams	56 (23.0%)
≥2500 Grams	174 (71.3%)
Apgar Score at 5 minutes	
<7	18 (7.4%)
≥7	226 (92.6%)

Table 5 reported the correlation between BMI and preterm delivery. The chi square p value for association between BMI and preterm delivery was 0.007 (<0.05), hence statistically significant. The spearman correlation coefficient r value for the strength of association was 0.710 (strong association).

Table 5: Association of Preterm Delivery with BMI (n = 122)

BMI Status	Preterm N (%)		Total	Chi Square	Spearman
	Yes	No			
Healthy (BMI=18.5-25Kg/m^2)	04 (11.1%)	32 (88.9%)	36	p-Value = 0.007	r Value = 0.710
Overweight (BMI=25.1-30Kg/m^2)	06 (23.1%)	20 (76.9%)	26		
Obese (BMI= >30Kg/m^2)	24 (40.0%)	36 (60.0%)	60		
Total	34 (27.9%)	88 (72.1%)	122		

Table 6 reported stratification of preterm delivery with various clinic-demographic parameters. None of the factors were shown to be significantly associated with preterm delivery. (P value > 0.05)

Table 6: Subgroup Analysis of Patients with Preterm Delivery (n = 122)

Variables	Preterm Delivery N (%)		Total	p-Value
	Yes	No		
Age (Years)				
<20	02 (25.0%)	06 (75.0%)	08	
20-29	12 (28.6%)	30 (71.4%)	42	0.966
30-39	16 (26.7%)	44 (73.3%)	60	
≥40	04 (33.3%)	08 (66.7%)	12	
Parity				
Nulliparous	18 (28.1%)	46 (71.9%)	64	0.947
Multiparous	16 (27.6%)	42 (72.4%)	58	
Previous Obstetrical Complications				
No	20 (28.6%)	50 (71.4%)	70	0.840
Yes	14 (26.9%)	38 (73.1%)	52	
Medical Comorbidities				
No	26 (30.2%)	60 (69.8%)	86	0.368
Yes	08 (22.2%)	28 (77.8%)	36	

DISCUSSION

The principal finding of our study shows a statistically significant association was observed between maternal obesity and the risk of preterm delivery in dichorionic twins with chi square p value 0.007 and spearman correlation coefficient r value 0.710 revealing strong correlation. This finding in contrast to the observation reported by Liu LY *et al.*, in their study where maternal raised BMI was not found as risk factor for preterm delivery in twin pregnancy as opposed to singleton pregnancy [13]. The difference in observation may be attributed to the fact that later study was carried out at Western population. The etiology of preterm delivery is multifactorial ranging from genetics to infections, trauma and fetal reasons. In this particular, apparently the genetics may have led to the difference in the results. Logistic regression analysis could have minimized this discrepancy. In a study carried out on Asian population by Li S and colleagues, reported findings in agreement with our observation which further supports assumption related to impact of genetic variability [14]. Maternal obesity was shown independent risk factor preterm delivery in the settings of multiple gestations by Suzuki S *et al.*, However, Sung and colleagues failed to report such association [15, 16]. The mean age of the patients in our study was 31.2 ± 5.96 years with almost half of the participants with dichorionic twins in the age group 30-39 years (n = 60, 49.2%). The pooled mean age of participants with twin pregnancies in a metanalysis by Santos S *et al.*, was 32.1 ± 5.33 years which is similar to our finding [17]. Seetho colleagues showed that majority of the patients with multiple gestation belong to the age group 20 to 34 years which is consistent with our finding [18]. The relatively high prevalence of multiple gestations may be attributed to the higher use of assisted reproductive medications in the fourth or fifth decade of life by women. Mean gestational age at the time of delivery in our study

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was 35.5 ± 1.7 weeks. In a study by Sung and colleagues, the mean gestational age at the time of delivery was 36.2 ± 2.9 weeks. Our findings corresponds to their observation [16]. Not only maternal obesity, several other factors impart their role to the gravity of the situation such as diabetes, hypertension, smoking and endocrine disorders [19]. The overall rate of preterm delivery in our study was 27.9% which is extremely higher than the global average of 10.6% which is another reason for concern [20]. The outcome of this research might perhaps be attributed to the study's setting, which is a low-income community lacking in sufficient resources and healthcare alternatives. The higher prevalence of preterm births observed in this study may be attributed to the association between preterm birth and maternal obesity as well as pre-existing medical conditions, as shown by prior research [19].

CONCLUSIONS

The study findings revealed that almost a third of dichorionic twins were delivered preterm. Majority of the patients were in third or fourth decade of life. Majority of the patients not had prior significant medical or surgical history. Statistically significant association was observed between the presence of maternal obesity and the occurrence of preterm delivery in dichorionic twins.

Authors Contribution

Conceptualization: MA
Methodology: J, MHB
Formal analysis: MA
Writing, review and editing: J

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparative Analysis of Functional Outcomes: Extramedullary Versus Intramedullary Fixation in Unstable Inter-Trochanteric Femoral Fractures

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ABSTRACT

Unstable trochanteric femoral fractures are challenging to manage. Two options exist for the operative treatment and management of unstable trochanteric fractures; i.e. extramedullary or intramedullary stabilization. However, there is a dearth of good evidence of the clinical efficacy of either of the two methods especially in terms of functional outcomes. **Objective:** To compare the functional outcome following fixation of unstable trochanteric femoral fractures via extramedullary versus intramedullary methods. **Methods:** This prospective cohort was conducted upon 46 adult patients and admitted at Liaquat University Hospital Hyderabad/Jamshoro, after taking written informed consent from parents. Functional outcomes utilizing the Timed Up and Go Test and Harris Hip Score, at 3 months and 6 months post-surgery and radiographic parameters were gathered to evaluate heterotopic ossification and femoral neck shortening at follow-up visits using a pre-structured questionnaire. The data was analyzed with SPSS V.21 and Microsoft Excel 2016. **Results:** The sample predominantly consisted of males, with a mean age of 31 ± 5 years. Intramedullary fixation showed superior early mobility outcomes and maintained better hip function scores compared to extramedullary fixation for unstable inter-trochanteric femoral fractures. Intramedullary fixation also demonstrated lower rates of heterotopic ossification and less femoral neck shortening, indicating potential benefits in reducing complications and preserving anatomical integrity. **Conclusions:** In conclusion, the study findings suggest intramedullary fixation as a favorable option for optimizing functional recovery and radiographic outcomes in such fractures.

INTRODUCTION

Managing trochanteric fractures presents significant challenges for trauma surgeons, encompassing issues ranging from nomenclature confusion to the absence of a standardized classification system and varying treatment approaches lacking consensus [1]. Moreover, dealing with an unstable trochanteric fracture adds complexity due to its biomechanically unfavorable nature. Accurate fracture classification, a pivotal step in treatment planning, typically starts with categorizing fractures as stable or unstable [2, 3]. Instability assessment often considers factors such as medial cortex comminution and posterolateral instability. The widely adopted AO/ASIF classification system divides trochanteric fractures into three primary groups. A1, A2 & A3. [4-6]. Treatment strategies for unstable trochanteric fractures commonly involve extramedullary or intramedullary stabilization methods [7, 8]. Extramedullary approaches typically involve utilizing sliding hip screws (SHS) attached to a plate at the lateral cortex, such as the Dynamic Hip Screw (DHS) or Compression Hip Screw (CHS). This method allows for

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direct open reduction of the fracture and is considered both safe and straightforward. On the contrary, intramedullary techniques entail percutaneously inserting a nail that is connected to neck screws capable of sliding through the nail. Examples include the Gamma Nail, Intramedullary Hip Screw (IMHS), and Proximal Femoral Nail (PFN) [9]. The minimally invasive nature of intramedullary fixation is associated with reduced blood loss and a lower infection rate. The implant should let patients put their full weight on it because it has good mechanical properties [10, 11]. However, there aren't many randomized clinical studies comparing intramedullary and extramedullary fixation methods for unstable trochanteric fractures, and the results of those that exist are inconsistent. Most studies compare these methods mainly for treating stable trochanteric fractures.

This comparative analysis was aimed to compare the functional outcomes of the two procedure following their use to treat unstable trochanteric fracture.

METHODS

This prospective cohort was conducted upon a sample of 46 adult patients, (divided into 2 equal groups of 23 each; labelled as A (Intramedullary group) and B (Extramedullary group), chosen via non probability convenience sampling, from January 2023 to June 2023. The study was approved by Research Ethics Committee of Liaquat University of Medical and Health Sciences (No. LUMHS/REC/-241, dated: 19/11/2022). Sample size was calculated using Open-Epi sample size calculator by taking mean time of 7.4 ± 3.83 vs 11.5 ± 5.71 sec for "Timed Up and Go Test" as functional outcome between intramedullary group vs extramedullary group, respectively, with confidence interval of 95% and power of study as 80%. [10]. Patients were admitted via both outpatient and casualty departments at Orthopedic of Liaquat University Hospital in Hyderabad/Jamshoro., after taking written informed consent from parents. Adults aged 18 to 45 years with unstable inter-trochanteric fractures were included in the study. Exclusion criteria included cases with poly-trauma, any pathological fracture, reverse oblique fractures or open fracture. Eligible patients were alternately assigned to either of the two study groups based on their admission sequence, ensuring each successive patient was allocated to a different group, thereby balancing group composition over time. The primary outcome variable assessed the success of surgery through functional outcome measurements, utilizing the Timed Up and Go Test and Harris Hip Score, at 3 months and 6 months post-surgery. Secondary outcomes included additional, specific radiographic parameters were gathered to evaluate femoral neck shortening and heterotopic ossification. Surgical success was determined by improved functional outcomes measured through the Timed Up and Go Test and Harris Hip Score at 3 and 6 months post-surgery. A decrease of more than 1-2 seconds in the Timed Up and Go Test, indicating improved mobility and a Harris Hip Score increase of 10 points or more reflects enhanced hip function and reduced disability following surgery. Secondary outcomes include radiographic assessments for femoral neck shortening, and heterotopic ossification, aiming for minimal complications and stable implant positioning post-surgery. Data was analyzed using SPSS v.21 and Microsoft Excel 2016. Comparative analysis between Group A and Group B was done via independent t-test for primary outcomes (Timed Up and Go Test, Harris Hip Score) at 3 and 6 months post-surgery. For secondary outcomes (radiographic parameters) frequency and percentage distributions was computed for heterotopic ossification while mean shortening was calculated for femoral neck shorting between groups.

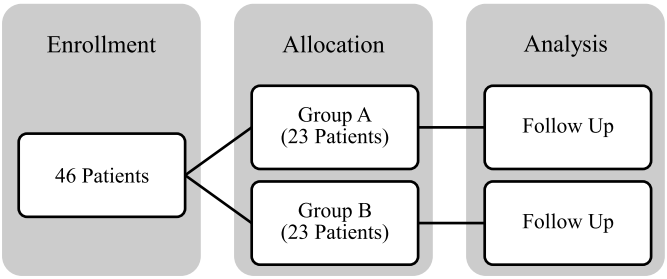

Figure 1: Patient Enrollment and Follow Up

RESULTS

A predominant majority of the sample comprised of males and the mean age of the sample stood at 31 ± 5 years as shown in table 1.

Table 1: Descriptive Statistics

Variables		Group A N (%)/Mean ± SD	Group B N (%)/Mean ± SD
Gender	Male	18 (78.3%)	21 (91.3%)
	Female	05 (21.7%)	02 (8.7%)
Mean Age (Years)		30 ± 5	32 ± 5

The results in table 2 showed that Group A (intramedullary fixation) had slightly better timed up and go test results at 3 months (12.5 ± 2.3 vs. 13.2 ± 2.1 seconds, p = 0.054) and significantly better at 6 months (10.8 ± 1.9 vs. 11.5 ± 2.0 seconds, p = 0.021) compared to Group B (Extramedullary fixation). Group A also showed higher Harris Hip Scores at both 3 months (85.2 ± 5.6 vs. 82.5 ± 6.3, p = 0.072) and 6 months (89.7 ± 4.8 vs. 88.3 ± 5.1, p = 0.193), although these differences were not statistically significant at 6 months. Overall, while Group A demonstrated better early mobility outcomes, both fixation methods yielded comparable improvements in hip function over the 6 months post-surgery period.

Table 2: Primary Outcomes-Functional Outcomes Measures

Variables	Group A (Mean ± SD)	Group B (Mean ± SD)	P-Value
Timed Up and Go Test (3 Months)	12.5 ± 2.3	13.2 ± 2.1	0.054
Timed Up and Go Test (6 Months)	10.8 ± 1.9	11.5 ± 2.0	0.021

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Harris Hip Score (3 Months)	85.2 ± 5.6	82.5 ± 6.3	0.072
Harris Hip Score (6 Months)	89.7 ± 4.8	88.3 ± 5.1	0.193

Table 3 outlines secondary outcomes for Groups A (Intramedullary fixation) and B (Extramedullary fixation) in unstable inter-trochanteric femoral fractures. Group A showed lower rates of heterotopic ossification (HO) stages, with 53.3% having no HO compared to 69.2% in Group B. Both groups exhibited minimal femoral neck shortening initially, but Group A maintained less shortening over time: 0.2 cm at 6 weeks, 0.2 cm at 3 months and 0.3 cm at 6 months, compared to Group B's increasing shortening to 0.9 cm, 1.0 cm, and 1.1 cm respectively. These results suggest potential benefits of intramedullary fixation in reducing HO and preserving femoral neck integrity compared to extramedullary fixation.

Table 3: Secondary Outcomes-Radiographic Parameters

Staining Of Heterotopic Ossification	Frequency N (%)	
	Group A	Group B
None	16 (53.3%)	18 (69.2%)
Stage-1	4 (13.3%)	2 (7.7%)
Stage-2	2 (6.7%)	1 (3.8%)
Stage-3	1 (3.3%)	2 (7.7%)
Duration vs Femoral Neck Shortening	**Mean Shortening (CM)**	
	Group A	**Group B**
6 Weeks	0.2	0.9
3 Months	0.2	1.0
6 Months	0.3	1.1

DISCUSSION

In this study, outcomes of intramedullary and extramedullary treatments were compared in a predominantly male sample with a mean age of 31 years. The findings revealed no statistically significant differences in primary or secondary clinical outcomes between the two treatment groups. However, radiographic assessments favored the intramedullary treatment group, showing less femoral neck shortening over time. Presently, treatment failure rates for intertrochanteric hip fractures range from 9% to 16%, often leading to successful union at the expense of considerable femoral neck shortening. Historically, implants aimed at restoring hip anatomy have shown high failure rates. However, intramedullary devices may offer biomechanical advantages due to their load-sharing nature, situated closer to the weight-bearing axis compared to plate-hip screw devices. Additionally, they tend to minimize femoral neck collapse [12-14]. Our study found significant differences in functional outcomes between Groups A and B for unstable inter-trochanteric femoral fractures. Group A, treated with Intramedullary fixation, showed better Timed Up and Go Test results at 3 months (12.5 ± 2.3 vs. 13.2 ± 2.1 seconds) and significantly better results at 6 months (10.8 ± 1.9 vs. 11.5 ± 2.0 seconds, p = 0.021). Group A also exhibited higher Harris Hip Scores at both 3 months (85.2 ± 5.6 vs. 82.5 ± 6.3) and 6 months (89.7 ± 4.8 vs. 88.3 ± 5.1), although the differences were not statistically significant at 6 months (p = 0.193). International research reveals similar trends favoring intramedullary fixation in improving functional outcomes for inter-trochanteric femoral fractures [15]. Studies from the United States and Europe, respectively, have demonstrated that intramedullary devices provide better stability and biomechanical advantages, which may contribute to enhanced post-operative mobility and hip function scores. However, international research also underscores the importance of patient-specific factors, surgical technique, and post-operative rehabilitation protocols in influencing outcomes [16, 17]. A meta-analysis found similar trends in favor of intramedullary treatment for femoral neck fractures, corroborating the radiographic findings of less femoral neck shortening observed in Group A of the current study [18]. Similarly, a retrospective cohort study conducted demonstrated comparable primary and secondary clinical outcomes between intramedullary and extramedullary treatments, aligning with the current study's findings [19]. However, studies did not specifically examine radiographic parameters, highlighting the unique contribution of the current study in assessing this aspect of treatment efficacy [20]. Conversely, a randomized controlled trial reported conflicting results, showing no significant differences in radiographic outcomes between intramedullary and extramedullary treatments for femoral neck fractures [21]. Additionally, literature suggests that other factors too play a role in the achievement of a good functional outcome. As surgeons gain more experience with different intramedullary fixation systems, treatment outcomes typically enhance, resulting in fewer intraoperative and postoperative complications. Making changes like adding specific options for locking screws at the end of bones has reduced how often bad things happen after surgery. Also, focusing on putting the fixation device exactly right in the hip bone after fixing the fracture well will help prevent the device from moving out of place. However, the current literature regarding intertrochanteric fracture treatment does not clearly favor one implant over another [22, 23].

CONCLUSIONS

In conclusion, intramedullary fixation showed superior early mobility outcomes and maintained better hip function scores compared to extramedullary fixation for unstable inter-trochanteric femoral fractures. Intramedullary fixation also demonstrated lower rates of heterotopic ossification and less femoral neck shortening, indicating potential benefits in reducing complications and preserving anatomical integrity. These findings suggest intramedullary fixation as a favorable option for optimizing functional recovery and radiographic outcomes in such fractures.

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Authors Contribution

Conceptualization: RAB, FM
Methodology: RAB, AHMJ, AA, LDM, AMH, FM
Formal analysis: RAB
Writing, review and editing: AHMJ, AA, LDM, AMH, FM

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

Frequency of C-Shaped Root Canals in Permanent Mandibular Second Molars in a Sample of Pakistani Population using Cone Beam Computed Tomography

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ABSTRACT

C-shaped root tubes have a challenging design that causes issues in the clinic. Endodontic therapy requires careful consideration of the C-shape root canal design in Pakistan due to the country's high carious rate (about 60%). **Objective:** To determine the frequency of C-shaped root canals in permanent mandible second molars among Pakistani adults. **Methods:** At Karachi's Altamash Dental Hospital, cross-sectional study was conducted between March 2021 and January 2022.We used mandibular CBCT images to analyze 302-second molars. The position of the longitudinal groove and the bilateral predominance of C-shaped root canals were also observed. A chi-square test was used for the statistical analysis. **Results:** 47 teeth (15.54%) out of 302 had a "C-shaped canal" configuration. The breakdown was as follows: 31.91% in Category 1 (C1), 14.89% in Category 2 (C2), 6.38% in Category 4 (C4), and 46.80% in Category 3 (C3). There was no appreciable variation in the prevalence of C-shaped canals between the genders; 32.14% of the patients had them unilaterally and 67.85% had them bilaterally. **Conclusions:** "C-shaped canals are found in 15.54% of the mandibular second molars" in the Pakistani sample group, and a high probability of a matching lingual groove (59.57%) is present in these teeth. The most common type of C-shaped root canals observed in this study is C3.

INTRODUCTION

In 1979, Cooke & Cox were the first to provide a detailed "Morphology of the C-Shaped Canal" described [1]. Clinically difficult treatment of C-shaped canals is caused by their complex architecture [2]. For effective endodontic therapy, then, it's crucial to have a solid grasp of the C-shaped root canal design. C-shaped root canals occur when the lingual and buccal sides of a tooth's epithelial root sheath are detached from the root surface [3, 4]. Mandibular second molars are often more closely associated with C-shaped root canals [1, 2]. "Mandibular premolars, mandibular first and third molars and maxillary molars may also have C-shaped root canals. It has been seen in previous data that the occurrence of C-shaped canals root is between 2.7% to 44.5%" [5, 6]. Prevalence studies indicate that C-shaped anatomy has a predilection toward the Asian population. East Asia has a larger frequency of the Asian people than South Asia [5, 7]. Roy A *et al.*, reported an overall prevalence of 37.39% in people of East Asian descent. Contrastingly, these authors reported a much lower prevalence of 6.7% to 7.5% in the South Asian population [7-9]. A few numbers of studies have used CBCT to look at the frequency of C-shaped root canals in the region of the mandible in South Asia [10, 11]. In a Pakistani population, C-shaped root canals in permanent "mandibular second molars" were assessed using CBCT. This imaging technique made it possible to precisely

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identify and assess the three-dimensional root canal form. C-shaped canals, which are complex and challenging to treat, were present in a large proportion of the sample [12, 13]. Endodontic diagnosis and treatment planning should include the following because to its prevalence: sophisticated imaging methods like CBCT, especially in populations with significant anatomical variances. Understanding these prevalence rates may enhance clinical results by guiding more precise endodontic operations.

By use of CBCT, this research sought to determine the frequency of C-shaped root canals in permanent mandible second molars in a sample of Pakistani adults.

METHODS

A cross-sectional research was done at Altamash Dental Hospital Karachi between March 2021 and January 2022. 2019 saw approval of this research by the Altamash Institute of Dental Medicine's ethical review committee (AIDM/ERC/2019/01/010). The formula for calculating the sample size for the research was "n= Z2 P (1-P) / d2. Z (statistic matching to confidence interval) is 2.576 at 99% confidence interval", d (precision) is 5% and P (prevalence) is 13%, where n is the sample size, as the research by Farid H *et al.*, revealed [12]. The estimated sample size was determined to be 302 mandibular second molars. CBCT scans of 151 Patients from Pakistan were sourced from the database of Altamash Dental Hospital. These scans were performed for diagnosis and treatment planning before dental implant placement. The selection of CBCT scans was based on the following criteria. The study includes mandibular second molars with complete root formation and bilaterally present, without previous restoration or endodontic treatment, and free of serious illness or history of head and neck trauma. Participants must have Pakistani nationality and access to standardized, high-quality cone beam computed tomography. Exclusion criteria was patients with known pathologies affecting general development or a history of endodontic treatment. Seventy-four of the 151 CBCT scans were of female patients, and the remaining 77 were of male patients. The patients ranged in age from 20 to 70. The data from these scans included 302 mandibular second molars (151 on the right and 151 on the left). The CBCT scans were performed with a DENTRI scanner. The CBCT images were analyzed using Will-Master image management software. Two clinicians examined CBCT images on two separate occasions with an interval of three months. The categorization of C-shaped root canals was done into four types: C1, C2, C3, and C4. These categories were determined by the presence and orientation of the longitudinal groove within the root canal system. Software used for data analysis was SPSS version 21.0. "The Chi-Squared test was used to look at the prevalence of C-shaped root canals based on age, gender, and tooth position". The occurrences of C-shaped root canals, both unilateral and bilateral, were also detected. "The C-shaped root canal system was categorized by Fan and associates. Statistical significance was set at p- value 0.05".

RESULTS

Total 302 teeth in table 1, 15.54 percent of mandible second molars had C-shaped canals in the roots this group had no C5 variations; 22 (46.80%) were classed as C3, 15 (31.91%) for C1, 7 (14.89%) as C2, and 3 (6.38%) as C4. Eighty-four percent of the 255 teeth preserved in their original state lacked C-shaped root canals.

Table 1: The Root Canal Distribution in Buccal Second Molar with and C-Type Morphology (n=302)

Root Canal Type	C-shaped Present N (%)	C1 N (%)	C2 N (%)	C3 N (%)	C4 N (%)	C5 N (%)	C-shaped Absent N (%)	Total N (%)
Total	47 (15.56%)	15 (31.91%)	7 (14.89%)	22 (46.80%)	3 (6.3%)	0 (0.0%)	255 (84.4%)	302 (100%)

In the table 2 seven teeth (14.89%) had a longitudinal groove; 28 (59.57%) had lingual root surfaces; and 12 (25.53%) had both lingual and buccal root surfaces. Nine (32.14%) patients had C-shaped root canals unilaterally, while 19 (67.85%) had them bilaterally (Table 2). Distribution Characteristics of C-Shaped.

Table 2: Root Canals in Mandibular Molars

Category	Subcategory	N (%)
Location of Longitudinal Groove	Buccal Groove	7 (14.89%)
	Lingual Groove	28 (59.57%)
	Both Buccal & Lingual	12 (25.53%)
	Total	47 (100%)
Unilateral and Bilateral Distribution	Male: Unilateral	3 (27.27%)
	Male: Bilateral	8 (72.72%)
	Female: Unilateral	6 (35.29%)
	Female: Bilateral	11 (64.70%)
	Total Unilateral	9 (32.14%)
	Total Bilateral	19 (67.85%)
	Total Cases	28 (100%)
	Chi-square (X^2)	0.197
	P-value	0.657

Figure 1 illustrated the bilateral incidence of C-shaped root canals.

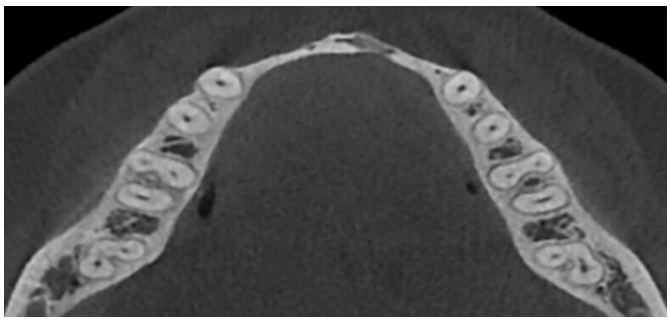

Figure 1: CBCT Axial Cross-Section Showing the Bilateral Occurrence of C-Shaped Root Canal Systems

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Figure 2 showed, meanwhile, that the patient genders did not vary statistically significantly. The bar chart displays the "frequency of C-shaped root canals among patients, both male and female". There were 47 teeth with C-shaped root canals; of them, 28 (89.57%) belonged to women and 19 (40.43%) to males. In contrast, 120 (47.06%) of the teeth in females and 135 (52.94%) of the 255 teeth in males did not have C-shaped root canals. The Chi-square test result (X2) of 2.4875 and the P-value of 0.114 indicate that there is no statistically significant difference in the frequency of C-shaped root canals in men and women. "This is seen by the correlation between the two variables".

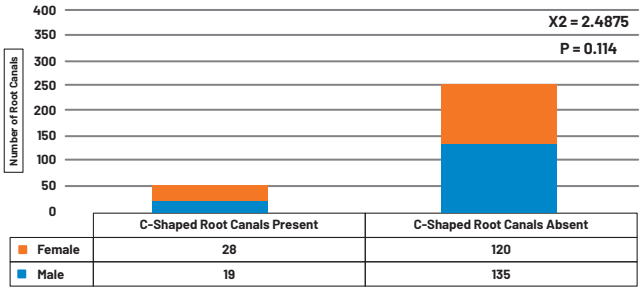

Figure 2: Gender-Specific Distribution of C-Shaped Root Canal Systems.

DISCUSSION

Previous research has shown that the total percentage of roots with C-shaped canals varies from 2.7% to 45.5% [1, 13]. In contrast, a recent research found that the frequency in the Korean population ranged from 31% to 44.5% [14]. The prevalence of c-shaped canals in Chinese may vary from 0.6%-41.27% [15]. Other parts of Asia have observed a lower frequency of this morphology of root canals Especially the South Asian population, including India and Sri Lanka, has shown to have a significantly low prevalence of this morphology. In India, Roy A *et al.*, reported a prevalence of 6.72% whereas, Wadhwani S *et al.*, documented a prevalence of 9.7% [8, 10]. The studies conducted in Sri Lanka report an even lower prevalence ranging from 1.9% - 2.9% as cited by Mazumdar P *et al* [15]. 15.54% of mandibular second molars had C-shape root canals, which is more than previously observed in the South Asian area [11]. Nevertheless, it is far lower than the prevalence in the Korean and Chinese populations. C-shape root canals are classified frequently according to the classifications proposed by a study [16]. The classification of the study does not provide a clear description of the difference between C2 and C3 root canals and their clinical significance. It also does not account for the anatomical changes of the root canal along the length [16]. Rana MA *et al.*, modified this classification using micro-computed tomography. Based on the geometry of their cross-section, they categorized the C-shaped root canals [17]. A more thorough explanation is given in this categorization [17]. The most prevalent C-shaped morphology was C3, which is consistent with studies done on Turkish and Portuguese people [18]. In this study, the tooth with a canal of C-shape had a lingual root and a longitudinal groove which is consistent with the researchers conducted in South Indian and Chinese populations by Yang L *et al* [19]. These findings are consistent with research carried out in India by Singh T *et al* [20]. These researchers found a higher percentage of C-shaped root canals in Indian females. The prevalence of C-shape root canals did not alter with age or position of the tooth in the present study which corresponds with previous studies conducted in different populations [21]. According to a study in 81% of people, a C-shaped root system found on one side is likely to be present on the opposite side. Similarly, C-shape root canals may be bilaterally present in over 70% of the cases [22]. This morphology is observed in 67.8% bilaterally in the present study. However, "there was no difference in bilateral occurrence according to gender". Studies assessing the anatomy of C-shaped root canals used radiography, cleaning procedures, histologic sectioning, and micro-CT scanning of the teeth. Moreover, it is challenging to recognize "C-shaped root canals" alone from radiographs. The tooth-clearing method and histologic sectioning are regarded as the gold standards for researching the anatomy of root canals [19, 20]. These methods permit analysis of the root canal anatomy from all dimensions. However, these methods destroy the specimen and are limited to ex-vivo examination. One such study, done in-vitro, conducted in Pakistan recently has recorded a prevalence of C-shaped canals of 9.5%. Their recoded number is lower than seen in this present study. A reason could be the limitation resulting from in-vitro assessment as the teeth available had to have been extracted previously due to some pathology and hence leading to limitations [16]. In recent years the trend has shifted towards using CBCT for assessment of root canal anatomy. "CBCT is a non-invasive imaging technique that provides three-dimensiona" and geometrically accurate images [19, 24]. Hence, it allows precise in-vivo visualization of the root canal anatomy making its use suitable for a prevalence study [19]. A study compared CBCT with Micro-CT and found two methods equally effective [21]. Studies have also shown that the accuracy of CBCT is greater than that of digital radiography [22]. Two studies conducted on the Pakistani sub population using CBCT show prevalence of 30 (10.2%) and 31 (10%) held in the province of Punjab, while this study held in the Province of Sindh shows a higher prevalence as ethnicity can been seen to cause anatomical variations [20, 21]. Another issue is an increased chance of strip perforation during root canal instrumentation, particularly along the thinner lingual walls [2, 3]. Nickel-titanium rotary instruments effectively debride root canals and reduce the risk of perforation. Anti-curvature filing technique should be utilized during root canal instrumentation to avoid stripping of the thin lingual wall. Avoiding Gates-Glidden burs for the preparation of

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mesiobuccal and buccal isthmus areas further minimizes the chance of perforation. Fine ultrasonic tips are more suitable for the preparation of isthmus areas' [23]. Mechanical instrumentation alone does not eradicate diseased pulpal tissue from the anatomically challenging parts of a C-shaped root canal. Therefore, cleaning the root canals with irrigation is necessary. Sodium hypochlorite is an effective irrigant with excellent antimicrobial and organic tissue-removing properties [24]. It can be ultrasonically activated to enhance effect. In addition, root canals should be irrigated with Ethylene-Di-Amine-Tetra-Acetic Acid (EDTA) dissolve the smear layer and inorganic stuff. Cold lateral compaction may be used for obturation of C-shaped root canals. However, cold lateral compaction produces less dense root canal filling and does not seal the buccal isthmus adequately method for the obturation of C-shaped root canals [25].

CONCLUSIONS

In Pakistanis, "C-shaped root canals in mandibular"second molars are very common (15.54%), and the lingual groove of the tooth is likely to match (59.57%), according to the research. The C-3 root canal is the most often occurring kind in this investigation. Sixty-seven percent of the time, a C-shaped root canal seen on one side was also seen on the contralateral arch.

Authors Contribution

Conceptualization: SNA
Methodology: SNA, SK
Formal analysis: MMM, SK
Writing, review and editing: MMM, MOA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Pattern of Fingerprints and Its Association with Gender among Medical Students of Peshawar Medical College

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ABSTRACT

Dermatoglyphics is the scientific discipline that studies the patterns and characteristics of fingerprints. When it comes to criminal justice and medical law, fingerprints are crucial. The analysis and comparison of unknown prints found at a crime scene with known prints of witnesses, victims, and possible perpetrators can greatly aid investigators and analysts in their pursuit of justice. **Objectives:** To identify fingerprint patterns and determine its association with gender among medical students of Peshawar. **Methods:** This cross-sectional descriptive study was conducted on students of Peshawar Medical College, Peshawar from 1st December 2021 to 1st June 2022. After a multi-stage proportional sampling process, a total of 300 students were included in the study, with 120 females and 180 males. After obtaining written agreement and adhering to stringent inclusion and exclusion criteria, students' fingerprints were placed on white paper using a stamp pad. The paper already bore the students' names, ages, sexes, and professional years. Statistical analysis was conducted using SPSS version 25.0, with descriptive and inferential statistics applied as necessary. **Results:** The most common fingerprint pattern was the loop pattern, followed by the whorl pattern at 30.33 percent. The average age of the participants in the study was 21.54 ± 2.33 years, with a male-to-female ratio of 1.5:1. All of the fingerprint patterns showed no significant association with gender. **Conclusions:** The study found that Loop fingerprints were more common than other fingerprints. Also, there is no statistically significant association between gender and fingerprints.

INTRODUCTION

Dactylography is the scientific investigation of fingerprints for identification. The theory holds that the skin on the balls of the fingers and thumbs has unique ridges that remain consistent throughout life. No two hands have the same pattern. Identification refers to the determination of a person's individuality. There are two sorts of individuality: complete and incomplete. Complete refers to an emphasis on distinct characteristics. Partial or partial identification involves determination of only little information about a person [1]. Extensive research has been conducted on the patterns and characteristics of fingerprints, highlighting their potential as indicators of individual traits and attributes. One particular area of interest is the investigation of the relationship between fingerprint patterns and sex, which has garnered significant attention among researchers. Understanding the association between sex and fingerprint patterns holds practical implications in forensic investigations, criminal profiling, and biometric systems [2]. The convenience, low cost, and high efficacy of fingerprints make them an ideal identification tool. A fingerprint is an imprint made by the flat of one or more fingers, and the pattern formed by these impressions is known as a fingerprint pattern [3]. A fingerprint is indicative of many different things.

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Hereditary, environmental, and other regional factors are among the many that influence fingerprints [4]. The skin on the hands and feet has a distinct texture and look compared to the rest of the body. The skin on the palmar and plantar surfaces is wrinkled and has small ridges called friction ridges. The ridges produced during the fetal stage do not change their course or alignment throughout an individual's life, until obliterated by the decomposition of the skin after death. [5]. Chromosomal syndromes cause changes in the body at t h e genetic level which lead to variations in fingerprint patterns. In Down syndrome (Trisomy21) there is a predominance of ulnar loops along with a large palmar crease, similarly, in Turner syndrome (45X0) whorls pattern is predominant [6]. There are four main categories of fingerprints: loop, whorl, arch, and composite. The ridge pattern determines if a fingerprint has an ulnar or radial loop, and the whorl pattern determines whether it has a circular or spiral pattern. Composite fingerprints can have four different patterns: plain, tented, central pocket loop, and twinned. Plain and tented arches are two subtypes of arch fingerprints. Fingerprints from extensively decomposed bodies can be extracted from the skin's dermis or, if the epidermis is removed, from the skin's epidermis. It is also possible to extract fingerprint prints from modified putrefied bodies (sometimes known as mummified mummies) by soaking the fingertips in a mild alkaline solution. With the use of contemporary technology, fingerprints can be transferred across continents or between nations [7]. Even with identical twins with strikingly comparable genetic makeup, the likelihood of identical fingerprints is quite low. About one in sixty-four million people have fingerprints that are identical to each other [8]. Dermatoglyphics is a useful non-invasive diagnostic tool that is widely utilized in anthropology, genetics, and medicine for early risk assessment of particular diseases [9]. During fetal life, the development of the primary ridges begins around the 12–16-week mark and is finished by the 24th week, or approximately the 6th month of gestation [10]. Since ancient times, people have used fingerprints as a form of identification. However, this study aimed to study pattern of fingerprints among medical students and its association with gender to gain insight into the expected gender based on fingerprint analysis.

The objective of this study was to identify fingerprint patterns and determine its association with gender among medical students of Peshawar

METHODS

From 1st December 2021 to 1st June 2022, a total of 300 students were included in this cross-sectional descriptive study at Peshawar Medical College, Peshawar by obtaining data collection permission letter with Reference No: PMC/PGMDE/369.

Sample size was calculated by using formula for finite population i.e $n=\frac{\frac{z^2 \times p\,(1-p)}{e^2}}{1+\frac{z^2 \times p\,(1-p)}{e^2 N}}$

(CI=95%, p=0.5%, e=0.05, N = population size that varies). Five equal clusters were made for the professional years of MBBS and in each cluster simple random sampling technique was applied. For randomization students roll numbers were taken. Research randomizer online was applied to select the sample randomly. Those students, who deny giving consent after being selected by randomizer, skipped and next available student was enrolled. Students of any age and gender from all professional years of Peshawar Medical College, Peshawar were included in our study. While Students with any hand deformity like permanent scars on fingers, any skin disease like leprosy, worn fingerprints and extra fingers were excluded. Fingerprints were taken on white paper using a stamp pad after the students' informed written agreement had been obtained. The paper already bore the students' names, ages, sexes, and professional years. Using a powerful hand lens (TAG3™ magnifying glass 50 Mm double reading glass optical graded lens with 5x and 10x magnifying capacity), primary patterns (loops, whorl, arches and composite) after fingerprints were procured. Each finger in the finger print slip was assigned a number, ex: The 1st number was assigned to the right thumb and 10th to left little finger based on the presence of ridge lines according to classification of Henry, s system (Henry's Ten Digit Classification).To conduct statistical analysis, the statistical package SPSS version 25.0 was utilized. When necessary, descriptive and inferential statistics were applied. For each possible association between gender and fingerprint pattern, we applied a chi-square test to see whether there was a statistically significant relationship ($p < 0.05$).

RESULTS

Our study included 300 students, with an average age of 21.54 ± 2.33 years. The gender ratio in the sample of 300 students was 180 (60%) males and 120 (40%) females. The table 1 shows that most common fingerprint pattern was loop pattern 164 (54.66%), followed by whorl pattern 91 (30.33%) and arch 28 (9.33%). In our study least common fingerprint pattern observed was composite 17(5.66%).

Table 1: The Pattern Distribution of Fingerprints

Fingerprint Pattern	Frequency (%)
Loop	164 (54.66%)
Whorl	91 (30.33%)
Arch	28 (9.33%)
Composite	17 (5.66%)
Total	300 (100%)

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The table 2 showed that loop pattern was most common in both sexes, followed by whorl, arch and composite respectively. There was no statistically significant association between fingerprint pattern and gender with a P value of more than 0.05.

Table 2: A Comparison of the Distribution of Fingerprint Patterns among Sexes and their Association with Gender

Fingerprint Pattern	Gender		p-Value
	Male	Female	
Loop	99	65	<0.288
Whorl	55	36	
Arch	18	10	
Composite	8	9	

DISCUSSION

Loop Fingerprint pattern was seen in 54.66 percent of the student's fingers, according to the study. Following that, 30.33 percent of the study's participants underwent a whorl fingerprint analysis. The average age of the participants in the study was 21.54 ± 2.33 years, and there were 1.5 times as many males as females. While there was no statistically significant correlation observed among gender and fingerprint patterns. Based on research carried out in Egypt 60 adults from Egypt and 60 from Malaysia were included in the study, with an average age of 22.37 ± 1.79 years, which is slightly older than the average age in the current research [11]. In a similar way another study conducted in Nigeria on a sample of 400 students mean age was recorded to be 21.86 ± 3.37 years, which is very close to what has been recorded in this study [12]. The participants' ages ranged from 18 to 25 years old, in contrast to a previous study in Lahore that included 150 students with ages ranging from 19 to 21 [13]. There is a 60% male prevalence in the results. Among 490 participants in a Nigerian study on gender predisposition, 51.8% were male, indicating a preponderance of males [14]. In another study conducted in Korea on 193 different participants, results revealed male dominance at 51.9% again similar to what has been reported in this study [15]. In contrast to the findings of this study, research conducted in Pakistan found that 70% of the students surveyed were female. The sample size was 100 individuals from Avicenna Medical College Lahore [13]. 62% of the male population was recorded in local research conducted in Abbottabad, which is nearly identical to the findings of this study According to the results, 54.66% of students had a loop fingerprint pattern, whereas 30.33% had a whorl print. [16]. Different studies worldwide have reported different numbers, in a study conducted in Nepal on a sample of 1960 participants, loop fingerprint was found to be most prevalent with 52.71%, followed by the Whorl type of fingerprint (27.38%) as reported in this study [17]. This research's findings are consistent with those of another Egyptian study in which 305 Libyan medical students ranked loop fingerprints highest (50.5% vs. 35.1%), which is statistically significant [18]. The results of yet another Nepalese investigation on 300 people showed that 51.13% of fingerprints were loops and 43% were whorls [19]. Similar to this study, another one published in the Journal of Ayub Medical College, Abbottabad similarly found that the most common fingerprint pattern in the city of Abbottabad was the loop pattern [16]. The research proved without a doubt that Loop is the most common fingerprint pattern. Our study found no significant association among fingerprints and gender. Similarly, another study found the same results [20-21].

CONCLUSIONS

Among medical students, the study found that loop fingerprints were more common than other fingerprints pattern. There was no statistically significant association between gender and fingerprints when looking at relationship statistics.

Authors Contribution

Conceptualization: FI
Methodology: NA, RSY
Formal analysis: AK
Writing-review and editing: NF, AA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Gingival Overgrowth in Patients Induced by Calcium Channel Blockers

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ABSTRACT

Gingival enlargement can be caused by a number of factors, including inflammatory conditions and the side effects of certain medications. Gingival overgrowth is one of the frequent features of gingival diseases. **Objectives:** To find out frequency of calcium channel blockers causing gingival overgrowth. **Methods:** A descriptive cross-sectional study was conducted among cardiac patients visiting the cardiology department at Liaquat University Hospital, Hyderabad by convenience sampling technique for a time duration of six months. SPSS version 23.0, was used for data analysis. Chi-square test was applied with a significance level of P-value <0.05. **Results:** The most commonly used calcium channel blockers were amlodipine and diltiazem at 31.3% and 26.7% respectively, while 15.6% of cases were using nifedipine, 14.4% were on verapamil and 11.9% were on calcium channel blocker drug of bepridil. The severity of gingival overgrowth was significantly correlated with the male gender (p value= 0.001). **Conclusions:** After administration of calcium channel blockers, there is a potential that adverse consequences may occur such as gingival overgrowth, will become more common by prolong use of such drugs as indicated in this study.

INTRODUCTION

An expansion of the gingiva (gums) is known as gingival enlargement. Several disorders, including inflammatory ones and the adverse effects of certain drugs, can lead to gingival expansion. This increase can be minor to exceedingly severe, localized, or generalized and it can be upsetting to the patient's look and function [1]. The term "hypertrophy" describes a rise in the size of individual cells, gingival enlargement is a more appropriate phrase to use since these identifications are not possible with a clinical examination and tissue assessment. The etiology of gingival enlargement has been divided into five broad categories: neoplastic enlargement, drug-induced enlargement, inflammatory enlargement, enlargement linked to systemic illnesses, and fake enlargement [2, 3]. Gingival hyperplasia can be caused by a variety of reasons, including medicines, periodontal variables and plaque management. Gingival enlargements are now linked to about 20 medications mostly anticonvulsants (like phenytoin), immunosuppressants (like cyclosporine A), and different calcium channel blockers (like nifedipine, verapamil, and diltiazem) [4]. Gingival enlargement is often significantly linked to dihydropyridine calcium channel

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blockers, such as nifedipine and felodipine" [5]. There are published statistics about the occurrence of Gingival Overgrowth (GO) in patients using nifedipine, even though the majority of the literature consists of case reports. Studies have shown that the incidence of this illness varies, with 20% to 83% observed for nifedipine-induced GO. Additional investigations showed that the prevalence of GO was 74%, 3.3%, and 21%, respectively, among amlodipine and verapamil calcium channel blockers diltiazem [6, 7]. Drugs known as calcium channel blockers treated heart-related disorders. Even while Calcium Channel Blockers (CCB) treatment is widely accepted in the medical world and is popular, its oral impact is rarely acknowledged or discussed. As a collective, CCBs have been repeatedly identified as a contributing component to a prevalent oral ailment observed in individuals undergoing dental cure: medication induced growth or expansion of the gingiva. There have been reports of varying prevalence rates (20% to 50%) for GO produced by CCB for nifedipine induced GO, whereas 3.3% was found for GO induced by amlodipine [8-10]. An increase in gingival mass and volume, which can be modest to severely severe, is its defining feature. The formation of an extracellular matrix in the gingival connective tissue, or CCB-induced gingivitis, usually starts within the first month of medication therapy [11]. Speech, mastication, tooth eruption, and aesthetics can all be negatively impacted by the abnormalities. These drugs frequently cause disfiguring gingival overgrowth, which makes it easier to have mouth infections, cavities, and periodontal disease [12-15].

Examining the gingival overgrowth was brought on by various calcium channel blockers that aimed for this study. It was beneficial for the knowledge of patients' cardiac practitioners regarding drugs of those calcium channel blockers that will be associated with gingival overgrowth to reduce morbidity.

METHODS

After approval of the study by the Institutional Research Ethics Committee LUMHS Jamshoro, a descriptive cross-sectional study was carried out at the cardiology department at Liaquat University Hospital Hyderabad using a non-probability convenience sampling approach during six months' duration was 1st June to 30th November 2018, (NO. LUMHS/REC/-681) dated 31-05-2018. All patients provided informed consent prior to their participation in the study. Patients visiting cardiac OPD and were using calcium blockers for more than 1 year were included in this study while pregnant women, patients with malignant disorders, and disabled persons were expelled from the study. The sample calculation was done using the Raosoft software, by using the proportion (20% of patients on calcium channel blockers are affected by gingival overgrowth) [12]. Margin of error was taken 5% and 95% confidence of interval, the sample size counted was 243. Miller and Damm classification of gingival overgrowth was used for describing the severity of gingival over growth was classified into four Categories as: Grade 0 = no gingival overgrowth, Grade 1 = mild over growth, blunting of marginal gingiva, Grade 2 = moderate overgrowth and Grade 3 = severe over growth bearing two-thirds of the tooth crown or where the whole attached gingiva affected. Based on a clinical examination, gingival overgrowth was confirmatively diagnosed. The SPSS version 23.was used for data analysis. Frequency calculations were performed for various variables and categorical factors, such as gender. The Chi-square test was applied to seek out the associations of different variables where P-value<0.05 was considered as significant.

RESULTS

Table 1 displays the participant's demographic information. Among a total of 243 participants, 159 (65.4%) were male and 84 (34.6%) were females, with ages between 40 and 60 years old where most of the subjects belonged to age 51-55 years (38.7%).

Table 1: Demographic Information of Study Subjects

Variables	(Mean ± SD) / N (%)
Mean Age	49.71 ± 5.25
Age (Years)	
40-45	60 (24.7)
46-50	55 (22.6)
51-55	94 (38.7)
56-60	34 (14.0)
Gender	
Male	159 (65.4)
Female	84 (34.6)

Patients were categorized as per duration of calcium channel blocker usage duration, most of the cases 43.6% were using it for more than 24 months, 30.5% were using calcium blockers from 19 to 24 months and 25.9% were using this medicine from 12 to 18 months as indicated in table 2.

Table 2: Duration, Type and Severity of Calcium Channel Blockers Use

Duration	N (%)
12-18 months	63 (25.9)
19-24 months	74 (30.5)
More than 24 months	106 (43.6)
Types of Calcium Channel Blockers	
Nifedipine	38 (15.6)
Amlodipine	76 (31.3)
Diltiazem	65 (26.7)
Verapamil	35 (14.4)
Bepridil	23 (11.9)

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Severity of Gingival Overgrowth	
Non/Grade 0	37 (15.2)
Mild/Grade 1	99 (40.7)
Moderate/Grade 2	78 (32.1)
Severe/Grade 3	29 (11.9)

As indicated in table 3, according to the type of the calcium channel blockers, the most commonly used calcium channel blockers were Amlodipine and Diltiazem 31.3% and 26.7% respectively, while 15.6% cases were using Nifedipine, 14.4% were on Verapamil and 11.9% were on the calcium channel blocker drug of Bepridil. As per evaluation of the severity of gingival overgrowth, the majority of the cases 40.7% and 32.1% had mild and moderate gingival overgrowth respectively, followed by 11.9% had severe gingival overgrowth and only 15.2% had no gingival overgrowth. The severity of gingival overgrowth was significantly correlated with male gender (p-value 0.001) as compared to females (p-value 0.014).

Table 3: Severity of Disease According To Drug and Gender

Calcium Channel Blocker	Severity of Disease N (%)				Total	p-Value
	Non	Mid	Moderate	Severe		
Nifedipine	28 (11.5%)	24 (9.9%)	7 (2.9%)	1 (0.4%)	60 (24.7%)	0.001
Amlodipine	5 (2.1%)	32 (13.2%)	15 (6.2%)	3 (1.2%)	55 (22.6%)	
Dilitiaem	4 (1.6%)	35 (14.4%)	44 (18.1%)	11 (4.5%)	94 (38.7%)	
Verapamil	0 (0.0%)	8 (3.3%)	12 (4.9%)	14 (5.8%)	34(14.0%)	
Bepridil	4 (1.6%)	12 (4.9%)	7 (2.9%)	6 (2.5%)	29 (11.9%)	
Gender						
Male	18 (7.4%)	60 (24.7%)	59 (24.3%)	22 (9.15%)	159 (65.4%)	0.001
Female	19 (7.8%)	39 (16.0%)	19 (7.8%)	7 (2.8%)	84 (34.6%)	0.014

DISCUSSION

A total of 243 patients of calcium channel blocker users were studied to assess the gingival hyperplasia. One of the common characteristics of gingival disorders is gingival overgrowth. However, the doctor finds it difficult to diagnose these entities because of their diverse manifestations. They can be divided into groups according to their location, size, extent, etiopathogenesis etc. According to the severity of gingival hyperplasia, the majority of the cases 40.7% and 32.1% had mild and moderate gingival hyperplasia respectively, followed by11.9% had severegingivalhyperplasiaandonly15.2% had no gingival overgrowth [16]. Since not all CCB patients have GO, it has been hypothesized that a subset of each patient's unique gingival fibroblasts may be the reason why gingival tissues are susceptible to the medications. Moreover, it was suggested that gingival fibroblasts, when subjected to the combined effects of pro-inflammatory cytokines like interleukin-1 β (IL-1β) which are higher in gingival inflammation boost the production of collagenous proteins [17]. Regarding the types of the calcium channel blockers, the most commonly used calcium channel blockers were Amlodipine and Diltiazem as 31.3% and 26.7% respectively, while 15.6% cases were using Nifedipine, 14.4% were on Verapamil and 11.9% were on the calcium channel blocker drug of Bepridil. Consistently Jayanthi R *et al.*, reported that the gingival enlargement occurred in 31% and 50% of the patients taking amlodipine [18, 10]. Increased fibroblastic proliferation and collagen synthesis result from the decreased calcium influx, which also reduces or inhibits the secretory function of the fibroblastic cells in question or collagenase production. The relationship between calcium and fibroblast may be strengthened by inflammatory alterations inside the tissue. On the other hand, Pilloni A *et al.*, reported that the among the calcium channel blocker users, 39 (67.2%) participants were on amlodipine, while 19 (32.8%) were on nifedipine [16]. Previous reports of nifedipine-induced hyperplasia have indicated the presence of an inflammatory response, indicating that strict hygiene protocols may limit the scope of the condition and slow its progression. In this study the severity of gingival overgrowth was significantly correlated with elevated age and male gender (p-0.001) and the severity of gingival overgrowth was significantly associated with the individuals, who were using calcium channel blockers from more than 24 months in contrast to less than 24 months (p-value 0.001) as indicated in table 3 While inconsistently Ganesh PR reported that no significant correlation between the length of time spent using CCBs and the incidence of Drug-Induced Gingival Overgrowth (DIGO) [19]. However, those with DIGO had a mean longer CCB usage history (63.2 ± 69.2) compared to those without DIGO (51.341.2) (P-value 0.416). It has been suggested that the presence of a subpopulation of gingival fibroblasts that are specific to each individual may be related to the gingival tissues' sensitivity to these CCB medications. Vidal F *et al.*, maintaining good dental health and receiving frequent professional prophylaxis are essential for maintaining the gingival tissue in patients with gingival overgrowth in a healthy state [20]. Similarly, Ganesh, P.R *et al.*, suggested that without altering the medications that cause gingival hyper growth, traditional periodontal therapy can produce acceptable clinical results [19]. After analyzing the course of therapy, which included scaling and root planning while under local anesthesia, elimination of any leftover pockets surgically and the installation of bridges to create a good occlusion, he came to this conclusion. Vidal F *et al.*, also mentioned the strong evidence supporting the appropriate management of gingival overgrowth brought on by phenytoin and calcium channel blockers by strict professional and personal dental care [20]. Dentists should be ready to treat patients with gingival overgrowth by focusing on patient education and periodontal care as well as preventative treatment. The damaged gingiva has an uneven and bulbous look, necessitating significant adjustments in the way oral hygiene treatments are provided. Due to the strong link between gingival overgrowth and plaque/gingivitis, dentists are essential in

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the prevention and management of this illness.

CONCLUSIONS

The study found that 43.6% of participants had been using calcium channel blockers, most common of which were Amlodipine (31.3%) and Diltiazem (26.7%). In terms of gingival overgrowth severity, 72.8% of participants experienced mild (40.7%) to moderate (32.1%) overgrowth, while 11.9% had severe overgrowth. Drug induced gingival enlargement is a multifactorial condition, and its risk factors can be grouped as systemic, genetic, drug and local.

Authors Contribution

Conceptualization: RK
Methodology: MAP
Formal analysis: JU
Writing, review and editing: JU, THS, SUUB, MAS, IP, RK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Urinary Neutrophil Gelatinase-Associated Lipocalin: A Biochemical Marker for Early Diagnosis of Urinary Tract Infections in Adults

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ABSTRACT

Urinary tract infection is an infection of the urinary system. Early diagnosis is helpful in timely treatment. Urinary NGAL is a new method that is used for early diagnosis of UTI. **Objective:** To evaluate the efficacy of urine neutrophil gelatinase-associated lipocalin (uNGAL) as a biochemical marker for early UTI diagnosis. **Methods:** A analytical study was conducted from Oct 2022 to Oct 2023, A total of 90 subjects having signs and symptoms of UTI irrespective of age and gender. The study participants were divided into three groups. Patients with UTI were included in diseased group (n=60) and healthy individuals were enrolled as controls in Group-I (n=30). SPSS v-26 was used for data analysis. Descriptive and Inferential statistics were applied. **Results:** The mean age of the participants was 30.5±6.9 years, 23(26%) were male, and 67(74%) female. These participants were divided into three groups; Group-I (control) had 30(33.3%) participants, group-II (patients with signs and symptoms but negative culture) had 34(37.8%), and group-III (patients with signs and symptoms and positive cultures) had 26(28.9%) participants. No growth was seen in participants of Group-I, II, and Group-III had positive cultures including *E. coli* (16.7%), *S. aureus* (10%), *Candida Sp.* (1.1%) and *Klebsiella Pneumonea* (1.1%) with significant findings (p<0.001). A significant difference among groups was noticed with uNGAL levels (p<0.001); Group-III had raised uNGAL levels of 361 ± 65.5ng/ml. **Conclusion:** Urinary NGAL is a promising biomarker that can detect UTIs even in the absence of clinical symptoms, enabling early diagnosis and treatment of UTIs.

INTRODUCTION

Urinary tract infections (UTIs) are common infections that happen when bacteria, often from the skin or rectum, enter the urethra, and infect the urinary tract. Usual signs and symptoms of lower UTI include pain or burning while urinating, frequent urination, feeling the need to urinate despite having an empty bladder, blood in urine, pressure or cramping in the groin or lower abdomen and/or fever (>38°c) [1]. On the basis of which parts are infected, UTI is either labeled as lower tract infection which includes urethra and bladder or upper tract infection which includes ureters and kidneys. UTI in adults is lower tract infection, caused by bacterial infection and typically treated using antibiotics [2]. The UTI can be divided into various types depending on type of causative agent and in terms of setting. UTI can be classified based on the causative agent, where it can result from either bacterial agents or fungi, with bacterial infection being the predominant type. In terms of settings from where the infection was acquired, UTI can be either hospital-acquired or community acquired in nature. Most of the UTI are uncomplicated but, in some cases, due to various reasons it can proceed to complicated infection [3]. In general, there are more than 150 million people annually getting bacterial UTIs acquired from community worldwide. It is also reported that UTIs are twice as common among women as compared to men, belonging to age group 18-39 years when sexual activity is

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common [4, 5]. In Pakistan the prevalence of UTIs in adults is reported to be 11.6% where prevalence in males was 8.9% as compared to 13.8% prevalence in the females. It was further reported that 20.7% of the positive cultures had growth of gram-positive bacteria while 79.3% had gram negative bacterial growth [6]. Urinary neutrophil gelatinase-associated lipocalin (uNGAL) based technique is a new method that can be used for early diagnosis of UTI. It is a protein identified from human neutrophil granules which is released as a part of innate immunity response to the infection in cells [7]. An extensive assessment of the literature revealed that, despite uNGAL's high level of reliability and diagnostic accuracy, no research has been conducted in Pakistan to examine its potential for the early detection of adult urinary tract infections. Furthermore, urine cultures frequently yield false-positive findings due to contamination. If a physician views a negative urine analysis (UA) result as adequate proof that a patient does not have a UTI, a urine culture exam may not be performed, increasing the likelihood that a UTI may go unnoticed. In the event that the patients took an antibiotic prior to the UA, a false negative result can also be shown [8,9]. Therefore, there is a need to explore the utility of this diagnostic technique to diagnose UTI in adult population of males and females in Pakistan.

The study aimed to ascertain whether urinary neutrophil gelatinase-associated lipocalin (uNGAL) is a valuable biochemical marker for early UTI diagnosis and to establish the ideal cut-off point for uNGAL based on sensitivity and specificity to diagnose UTIs in the adult population.

METHODS

A descriptive-analytical study was conducted in the Department of Chemical Pathology in collaboration with the Medicine/Surgery Clinic at Pakistan Railway Hospital, Islamic International Medical College, Rawalpindi, Pakistan. The study was conducted after taking proper consent from patients and approval from the ethical review board committee (IRB-Riphah/IIMC/IRC/22/2064. Dated; October 04, 2022) from Oct 2022 to Oct 2023 through a non-probability consecutive sampling technique. The sample size was calculated by using the WHO sample size calculator using Cochran' formula by considering 11.6% prevalence was 160 [6]. However, a total of 90 subjects were included in this research due to financial constraints and limiting factors. The diseased group (n=60) consisted of male and female adult patients (>18 years old) who had symptoms of fever (>38°C), pain or burning during urination, frequent urination, feeling the need to urinate even though their bladder was empty [6]. Thirty healthy individuals were included as controls, regardless of gender or age (>18 years) were included in the inclusion criteria. The Patients diagnosed with diabetes, renal dysfunction, recurrent UTI, pregnant females, patients taking antibiotics, and diagnosed with some other related infection were added to the Exclusion Criteria. Healthy individuals were enrolled as control. Patients presented with signs and symptoms of UTI were enrolled in the diseased group (n=60). Demographic data and clinical parameters including age, gender, weight, height, clinical signs and symptoms, duration of symptoms, presence of blood in urine, history of clinical comorbidities, and medication history were recorded on the pre-designed data collection proforma. 5ml blood was drawn from each patient for laboratory investigations. The sample was transferred to a plain bottle for serum collection and it was centrifuged at 3000 rpm for 5 minutes at -20 degrees centigrade. From collected blood samples, serum creatinine, serum urea, and Creactive protein (CRP) laboratory testing was done. The patients were asked to provide 20 ml of clean-catch midstream sample of urine ensuring aseptic measures for urinalysis (urine R/E), which included: physical examination, microscopy, and urine dipstick test. Urine culturing was done by spreading urine samples on MaConkey, blood, or chocolate agar plate and incubating at 35-37°C for 18-24 hours followed by identification tests including gram staining, biochemical testing, and microscopic examination. For uNGAL, the urine sample was centrifuged for 20 minutes at the speed of 2000-3000 r.p.m then samples were proceeded for identification by using NGAL ELISA Kit. Patients of diseased group (n=60) were further categorized into two groups based on culture report. uNGAL levels were compared among the three groups. Data were kept confidential and anonymity of the study participants was maintained. SPSS version 26.0 was used for data entry and analysis. Descriptive statistics (frequencies % and mean ± SD) were computed. Pearson's Chi-square test and one-way ANOVA were applied to compare the variables among three study groups. p-value <0.05 was considered significant by taking a 95% confidence interval.

RESULTS

Mean age of 90 participants was 30.5 ± 6.9 years, 23 (26%) were male, and 67 (74%) were female participants. Based on urine culture report, study participants of diseased group were categorized. 26 (29%) patients in diseased group had a positive urine culture. Sample of a patient had a positive urine culture (Figure 1).

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Figure 1: Urine Culture Sample of a Patient on Mcconkey Agar Plate

The study participants were divided into three groups. In Group I Healthy adults without signs and symptoms of UTI and with normal urine routine examination (Controls) (n=30). In Group II Patients with signs and symptoms of UTI with negative urine culture (n=34). In Group III Patients with signs and symptoms of UTI with positive urine culture (n=26) (Figure 2).

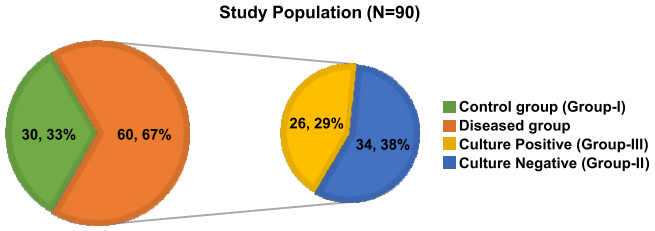

Figure 2: Distribution of Study Population based on Signs and Symptoms of UTI and Urine Culture

No growth was seen in participants of Group I, II and III had positive cultures including *E. coli* (16.7%), *S. aureus* (10%), *Candida Species* (1.1%), and *Klebsiella Pneumonia* (1.1%) with significant findings (p<0.001)(Figure 3).

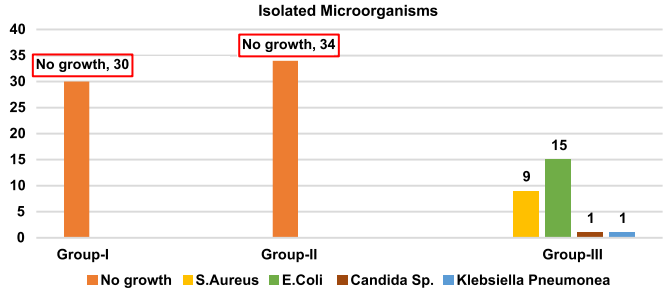

Figure 3: Comparison of Study Groups with Isolated Microorganisms

Urinary NGAL levels were categorized as normal and high <300 ng/ml and ≥300 ng/ml respectively. 92.3% (n=24) patients of Group-III had higher level of uNGAL (361 ± 65.5ng/ml) as compared to other groups. A statistically significant findings were observed with uNGAL among the study groups (p<0.001)(Figure 4).

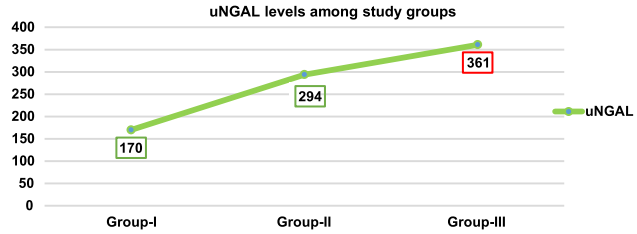

Figure 4: Comparison of Study Groups with Mean uNGAL Values

The majority of the study participants (81%, n=73) belonged to lower socio-economic status, and the majority (42%) had under-matric education. The mean urine creatinine was 81 ± 14.5 mg/dl, the mean serum urea was 32.5 ± 6.8 mg/dl, mean CRP value was 10.2 ± 3.9, and mean value of serum creatinine was found to be 0.9 ± 0.5 mg/dl. The mean uNGAL value among study subjects was 272.3 ± 93 ng/ml (Table 1).

Table 1: Demographics and Clinical Parameters Among Study Groups

Study Variables			Group I (n=30)	Group II (n=34)	Group III (n=26)	p-Value
Gender	Male		3 (10.0%)	12 (35.3%)	8 (30.8%)	0.053
	Female		27 (90.0%)	22 (64.7%)	18 (69.2%)	
Socio-Economic Status	Middle Class		13 (43.3%)	1 (2.9%)	3 (11.5%)	<0.001
	Lower Class		17 (30%)	33 (34%)	23 (26%)	
Educational Status	Under Matric		3 (10%)	16 (47%)	19 (73%)	0.003
	Matric / SSC		8 (26.7%)	4 (11.8%)	4 (15.4%)	
	Hssc / Intermediate		17 (56.7%)	13 (38.2%)	3 (11.5%)	
	Graduation		1 (3.3%)	1 (2.9%)	-	
	Masters		1 (3.3%)	–	-	
Sign and Symptoms	Pain and / or Burning While Urinating		-	34 (100%)	26 (100%)	<0.001
	FrequentUrination		-	17 (50%)	26 (100%)	<0.001
	Feeling the Need to Urinate		-	33 (97.1%)	26 (100%	<0.001
	Pressure or Cramping in the Groin Abdomen		-	31 (91.2%)	26 (100%)	<0.001
	Fever (>38 degree C)		-	34 (100%)	26 (100%)	<0.001
	Blood in Urine		-	16 (47.1%)	13 (50%)	<0.001
Urine R / E	Leukocyte Esterase		-	12 (35.3%) (5+, 7++)	16 (61.5%) (6+, 10++)	<0.001
	Nitrite		-	-	1 (3.8%)	
	Pus Cells	<5	30 (100%)	18 (52.9%)	6 (23%)	
		>5	-	11 (32.35%)	12 (46.1%)	
		Numerous	-	5 (14.7%)	8 (30.8%)	
Isolated Micro - Organisms	No growth		-	34 (100%)	-	<0.001
	S. aureus		-	-	9 (34.6%)	
	E. coli		-	-	15 (57.7%)	
	Candida Species		-	-	1 (3.8%)	
	Klebsiella Pneumonea		-	-	1 (3.8%)	

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uNGAL Levels	Normal (<300)	30 (100%)	17 (50%)	2 (7.7%)	<0.001
	High (<=300)	-	17 (50%)	24 (92.3%)	

Pearson's chi-square test and one-way ANOVA were applied to measure significance. A significant difference among groups was noticed with gender (p=0.053), socio-economic status (<0.001), educational status (0.003), signs and symptoms of UTI (<0.001), urine R/E (<0.001), serum creatinine (0.031) and uNGAL levels (<0.001) (Table 2).

Table 2: Comparison of Study Groups with Age and Laboratory Findings by One-Way ANOVA

Study Variables		Mean ± S.D	Test of Homogeneity of Variances		ANOVA	
			Levene's Statistic	Sig.	F	Sig.
Age	Group-I	31.03 ± 8.42	2.547	.084	.289	.750
	Group-II	29.76 ± 6.48				
	Group-III	30.73 ± 5.65				
Urine Creatinine (mg/dl)	Group-I	64.33 ± 7.01	2.324	.1041	.621	.204
	Group-II	99.24 ± 127.45				
	Group-III	76.45 ± 13.08				
Serum Urea (mg/dl)	Group-I	30.6 ± 5.10	3.681	.0293	.022	.054
	Group-II	27.67 ± 7.63				
	Group-III	41.19 ± 39.26				
Serum Creatinine (mg/dl)	Group-I	0.72 ± 0.13	4.477	<0.001	9.782	<0.001
	Group-II	0.89 ± 0.29				
	Group-III	1.26 ± 0.79				
CRP (mg/dl)	Group-I	2.43 ± 0.60	10.034	.0142	.023	.138
	Group-II	6.12 ± 7.22				
	Group-III	24.45 ± 80.72				
uNGAL (ng/dl)	Group-I	170.46 ± 10.63	15.9	<0.001	97.990	<0.001
	Group-II	294.17 ± 61.78				
	Group-III	361.26 ± 65.55				

DISCUSSION

The purpose of this study was to demonstrate the usefulness of urinary neutrophil gelatinase-associated lipocalin (uNGAL) as a biochemical lab test for an early and accurate diagnosis of UTI in adult population in order to rationalize the empirical use of antibiotics and to define its optimal cutoff point based on sensitivity and specificity for diagnosing UTI in adults. Study population (n=90) was divided into three groups based on signs and symptoms and urine culture reports. In our study, the frequency of UTI was higher in lower socioeconomic status (81.1%) and in lower educational status (73%) groups, which is supported by another study [10]. Likewise, Casey *et al.*, in 2021 suggested that financial situation cannot be considered as a prime factor but considered a phenomenal factor in enhancing the rate of UTI [11]. Other studies reported that educational level and socioeconomic status are the significant contributing factors of UTI [12, 13]. In our study, out of diseased patients, 66.7% reported fever and pain/burning during urination. According to Jagadesan *et al.*, fever was the most common symptom in UTI patients [14]. In our study on complete urine examination, 76.9% patients of group-III and 47% of group-II patients had >5 pus cells/HPF or numerous pus cells/HPF, while control group had <5 pus cells/HPF or no pus cell. Similar to our findings Alateeq *et al.*, reported that majority patients of non UTI group either did not reveal any pus cells or had less than 5 WBCs/HPF, While, UTI group, had >5 or numerous pus cells/HPF on urine routine examination [15]. Our study reported the positive culture in 26(28.9%) patients, with the most prevalent strains of *Escherichia coli* 15(57.7%) among other bacterial agents causing UTI, followed by S. Aureus 9(34.6%) while Candida Species and *Klebsiella Pneumonea* were isolated in only 1(3.8%) patients. Similar to our findings Mashaly *et al.*, also reported that E. coli was the highest prevalent (62%) among all positive cultures, while *Klebsiella Sp.* represented the 2nd most common organism (12%) [16]. According to Krzemień *et al.*, *E. coli* was in 52 (96.3%), *Klebsiella Sp.* in one patient [17]. In line with their findings Jagadesan *et al.*, stated 34% culture-positive UTI patients in their study with the predominant organism was *E. coli* (82%), followed by *Enterococcus Sp.* (9%) and Klebsiella Sp. (6%) [14]. Our research indicates that a higher level of uNGAL (≥300 ng/dl) was present in 92.3% (n=26) of group-III patients (patients with UTI), with a mean value of 361.26 ± 65.5 ng/dl. According to a study, uNGAL levels were higher in the UTI group than in the non-UTI group in multivariate analysis (p<0.05) [18]. A recent meta-analysis showed that urinary NGAL had a high diagnostic value in detection of UTI [19]. In a meta-analysis, researchers found that NGAL was more accurate for the diagnosis of UTI [20]. In a recent study, urinary NGAL levels were found to be significantly higher in patients with bacterial UTIs compared to those with non-bacterial UTIs or controls. These findings suggest that urinary NGAL can be used to differentiate between bacterial and non-bacterial UTIs, which is important in guiding appropriate treatment. It also suggests that raised uNGAL levels in other negative culture groups were due to the non-bacterial UTI [21]. Furthermore, according to a study, reduced levels of urinary NGAL were because of the recurrence of UTI and could serve as a biomarker [22]. Few studies have claimed that uNGAL is not helpful in the diagnosis of UTI, which contradicts our findings. When an author compared the NGAL level of UTI patients to that of healthy controls, he did not detect a significant difference. This could be because of the lack of inflammation or the existence of renal injury in UTI patients. Larger studies, according to the researcher, might validate the use of uNGAL as a biomarker in the context of infection and determine the best cut-off values [23]. According to many researchers, it was observed that uNGAL levels significantly decrease in patients having antibiotic treatment [17]. Urinary NGAL level patterns in recurrent UTIs seem to differ from those in first UTI episodes. Forster *et al.*, for instance, demonstrated that NGAL levels may be lower in patients with recurrent UTI compared with those

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without. Patients in the control group had lower median NGAL concentrations than recurrent UTI group, while patients with single UTI had higher NGAL value [24]. Of course, little is known about it so, further studies are needed to reach a definite assumption. The risk of bias regarding patient selection and flow and timing was high and unclear in few studies. This may be due to the difference in study designs [19]. Despite the promising results of studies investigating the diagnostic and prognostic applications of uNGAL in UTIs, the cost and availability of uNGAL assays may limit their widespread use in clinical practice [25]. Another factor is the lack of a standardized uNGAL assay. There are currently several uNGAL assays available. This can lead to variability in the diagnostic accuracy of uNGAL [26]. Literature suggests that uNGAL can be used for early diagnosis and can predict the severity of UTIs and guide appropriate treatment. Despite the promising results of many studies further research is required to validate its diagnostic accuracy in early diagnosis of UTIs. Future longitudinal studies should investigate the use of uNGAL in different patient populations and in different clinical settings.

CONCLUSIONS

It is concluded that Urinary NGAL is a promising biomarker that can detect UTIs even in the absence of clinical symptoms, enabling early diagnosis and treatment of UTIs. An early and reliable diagnosis of UTI with uNGAL can help in avoiding the unnecessary use of antibiotics in patients diagnosed with UTI. However, further research is necessary to validate its diagnostic accuracy and to determine its optimal use in different patient populations.

Authors Contribution

Conceptualization: MNAK
Methodology: SS
Formal analysis: HMAA, SQ
Writing-review and editing: MNAK

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Knowledge of Gestational Diabetes Mellitus Among Diabetic Pregnant Females

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ABSTRACT

The prevalence of Gestational Diabetes (GDM) is rising quickly and patients require assistance with decision-making, behavioral control and obtaining the knowledge required for self-care. The knowledge of GDM, together with nutritional guidance and glycemic control education, is crucial to the care of diabetic women. **Objective:** To determine the knowledge among gestational diabetic pregnant females. **Methods:** A cross sectional study was conducted at obstetrics and gynecology outpatient departments in Department of Obstetrics and Gynecology, Niazi Medical and Dental College, Sargodha. 150 pregnant females aged range (18-40) year, with any gravida and diagnosed with GDM were enrolled in current study. A structured questionnaire regarding the knowledge of gestational diabetes was used to collect data. Data were entered and analyzed in Statistical Package for Social Sciences (SPSS) version 21.0. **Results:** Majority of participants were 18-30 years 80 (59.3%) old. 42 (28%) were normal weight, 82 (54.6%) were overweight and 26 (17.3%) were obese while 98 (65.3%) women were housewives. 63 participants know about self-care routine of GD, while 58 know about feto-maternal complications. Majority 90 (60%) females don't know about the risk and symptoms of gestational diabetes. 101 (67.3%) have poor knowledge about glucose monitoring. When they asked about the management of hypo and hyper glycemia 81(54%) don't have enough knowledge about management protocols. Regarding the diagnostic procedures 74 (49.3%) have good knowledge. **Conclusions:** The study concluded that most participants, have lack of knowledge of GDM, management of Gestational Diabetes Mellitus (GDM), its symptoms, fetomaternal complications and diagnostic criteria..

INTRODUCTION

Gestational diabetes is a global public health concern [1]. In 2019, 223 million females are predicted to develop diabetes. The population this disease is expected to reach 343 million by 2045. 20 million live births or 16% of all births, were impacted by a specific type of pregnant hyperglycemia. It is believed that 84% of cases are caused by gestational diabetes. One in six babies had gestational diabetes [2]. Pregnant hyperglycemia most frequently occurred in low and middle-income countries, when access to maternity care is typically restricted [3]. The prevalence of GDM is rising quickly and is expected to keep rising in light of the global obesity pandemic. Through genetic and environmental factors that are yet not fully understood, GDM has substantial negative effects on the health of both the present and future generations. The condition also places a heavy financial burden on healthcare systems, with variations in clinical approach frequently being dictated by resource constraints. Uncertainty exists over the ideal period for screening and diagnostic GDM thresholds [4]. Every woman has a special period during her pregnancy. When GDM is diagnosed, which necessitates controls and therapies that will unavoidably impair the woman's life, the condition becomes even more delicate. GDM can result in clinically significant detrimental consequences on the mental health of the mother, including a reduced quality of life, as well as dangers for the development of fetus [5]. In Pakistan, Gestational Diabetes Mellitus (GDM) poses

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significant health risks, increasing hypertension, cesarean delivery, and future diabetes in mothers and causing complications like macrosomia and neonatal hypoglycemia in children. Factors such as lack of awareness, limited healthcare access, traditional diets and genetic predispositions contribute to these risks. Preventive measures include early screening, promoting healthy lifestyles, public education, and improving healthcare accessibility [6]. The disease is mostly unrecognized in Pakistan since there is a lack of relevant information about its risk factors and preventive measures. According to conflicting data from Pakistan, the incidence varied widely by city, reaching as high as 36% in Peshawar, 22% in Karachi, 37% in Lahore, 20% in Balochistan, 14% in Bahawalpur, and 14.8% in Hyderabad [7]. GDM is a severe and risk to the health of mothers and children. Many females with GDM experience pregnancy-related issues such high blood pressure, premature birth and labor obstruction. Nearly half of women with a history of GDM develop type 2 diabetes within five to ten years of giving child. Adverse pregnancy outcomes are linked to gestational diabetes mellitus [8]. Due to the GDM clinical treatment procedure complexity, both the mother and the fetus are at risk. Exploring GDM risk factors can therefore help to lower the frequency of perinatal problems [9]. Self-care is a concept that needs more research in women with GDM because it is influenced by cultural norms and personal views [10]. Self-care is less common in women with GDM, which may be a result of the lack of educational resources available to diabetic clinics and health centers due to a lack of awareness of self-care strategies [11]. GDM patients require assistance with decision-making, behavioral control and obtaining the knowledge required for self-care. Self-management of GDM, together with nutritional guidance and glycemic control education, is crucial to the care of diabetic women. An essential component of managing and controlling gestational diabetes is self-efficacy [12]. According to reports, pregnant women who lack self-care knowledge about GDM and its complications lengthen their stays in hospitals [13]. Providing clear GDM education on self-care and managing complications for pregnant women can reduce complications and shorten hospital stays [14]. Teaching the patient how to self-monitor and log their own glucose and ketone readings at home is a crucial component. Health education is one of the strategies to provide women with the knowledge and skills to facilitate self-care, which is a key aspect of managing GDM to achieve the best possible outcome for the mother and child, since it is the first cornerstone step for good diabetes control.

The present study was conducted to determine the self-care knowledge among gestational diabetic pregnant females.

METHODS

A cross sectional study was conducted in department of obstetrics and gynecology Niazi Medical and Dental College, Sargodha after taking the approval from institutional review board of Niazi Medical and Dental College Sargodha, IRB number, NM&DC/IRB/91 and reference number, NM&DC/IRB/409. The duration of study was 15th September to 30th December 2023. The sample size of 150 was calculated by taking expected percentage of self-care knowledge of GDM among pregnant females as 26.2%, by taking 95% confidence interval and 7% margin of error [15]. After taking the written and informed consent all the pregnant females aged range 18-40 years, with any gravida and diagnosed with GDM were enrolled by convenient sampling technique in current study. The females with type 1 or type 2 diabetes mellitus pregnancy with more than one fetus, known major fetal anomaly, Current or planned corticosteroid therapy and females from medical background were excluded from current study. A structured questionnaire regarding the knowledge of gestational diabetes was used to collect data. This was measured through 18-items multiple choice questions adopted from knowledge questionnaire. The correct answer for knowledge was given a score of "1" and incorrect given "0" [16]. The questionnaire also consists of information regarding risk factors, symptoms, effects on pregnancy, including diagnostic procedures required to rule out GDM, treatment plans, and women's sources of information on the condition. Each correct answer was marked as 1 and incorrect as 0. The score ranges from 0-18. The score more than 8 was consider as good knowledge and score <8 was considered as poor. and Data were entered and analyzed in Statistical Package for Social Sciences (SPSS) version 21.0. For quantitative variables, mean and standard deviation was computed. For qualitative variables, frequencies and percentages was computed.

RESULTS

Table 1 illustrated the demographic data of participants. Regarding the age majority of participants were 18-30 years 80 (59.3%) old and remaining were 31-40 years 61 (40.6%), In regard to the BMI (Body Mass Index) of the pregnant women, the findings of the present study documented that 42 (28%) were normal weight, 82 (54.6%) were overweight and 26 (17.3%) were obese. Regarding the educational level table also shows that (24.6%) were illiterate, while (36%) have secondary education, (41%) had intermediate education and only 12% were graduated. According to occupation, 98 (65.3%) women were housewives and the rest of them were working. While 34.0% husbands' occupation was laborer and most of them 58% were Jobian, only 8% were unemployed. On the other hand, females with the strong family history of DM as the most frequently encountered risk factors of GDM that was

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confirmed by 97(64.6%)as shown in table 1.

Table 1: Socio-Demographic Characteristics of the Intervention and Control Group

Variables	N (%)
Age (Years)	
18-30	89 (59.3%)
31-40	61 (40.6%)
BMI	
Normal Weight	42 (28%)
Over Weight	82 (54.6%)
Obese	26 (17.3%)
Education Level	
Illiterate	37 (24.6%)
Secondary	54 (36%)
Intermediate	41 (27.3%)
Graduation	18 (12%)
Female Occupation	
Housewife	98 (65.3%)
Working	52 (34.6%)
Husband Occupation	
`Labour	51 (34.0%)
Job	87 (8%)
Unemployed	12
Family History Of Diabetes	
Yes	97 (64.6%)
No	53 (35.3%)

As shown in table 2, it indicates that majority females (62.0% respectively) were multigravida. Also table 2 showed that majority females had more than 1 parity. As regard to the type of last delivery, slightly more than half (58.6% respectively) of women among delivered by cesarean section.

Table 2: Reproductive History of the Participants

Variables	N (%)
Praimrigrvida	57 (38.0%)
Multigravida	93 (62.0%)
Parity	
Nullipara	21 (14.0%)
1-3	82 (54.6%)
>3	47 (31.3%)
24 -26 Weeks	61 (40.6%)
27-28 Weeks	89 (59.3%)
Previous History of GDM	
Yes	55 (36.6%)
No	95 (63.3%)
Caesarean Section	88 (58.6%)
Normal Vaginal Delivery	62 (41.3%)

Table 3 illustrates the knowledge about gestational diabetes among pregnant females. According to the data, 63 participants (42%) are aware of the risk factors associated with GDM, and 58 participants (38%) are knowledgeable about feto-maternal complications. However, 92% of participants have poor knowledge in these areas. When it comes to the management of GDM, 101 participants (67.3%) lack sufficient knowledge. Regarding diagnostic procedures and treatment plans, 74 participants (49%) have a good understanding. Overall, 62 participants (42%) possess good knowledge of GDM (Table 1).

Table 3: Knowledge about Gestational Diabetes among Pregnant Females

Variables	Frequency	Percentage of Knowledge
Knowledge about Risk Factors (Yes/No)	63/87	42%
Knowledge about diagnostic Criteria and treatment Plan (Yes/No)	74/76	49%
Knowledge about feto-maternal Complications (Yes/No)	58/92	38%
Management of GDM (Yes/No)	49/10	32.6%
Overall Knowledge (Yes/No)	163/87	42%

DISCUSSION

Prenatal care plays a crucial role in minimizing risks and fostering favorable outcomes for both mothers and fetuses. It empowers expectant women by equipping them with essential knowledge and skills while boosting their physical and mental well-being [17]. Interventions focusing on lifestyle adjustments in the early stages of pregnancy empower women, enhance their self-care practices and mitigate potential negative consequences [18]. A study involving 85 pregnant women in the United States aimed to evaluate their knowledge and beliefs during their initial prenatal appointment. It revealed that half of the participants had insufficient understanding of Gestational Diabetes Mellitus (GDM), including its risks, treatment options, causes and potential outcomes. Notably, some attributed GDM to inheritance, environmental factors and hormonal changes, indicating a lack of awareness. These women also expressed a need for medical intervention to manage associated complications. These findings were relevant to the current study, which indicates that 54% have poor knowledge and majority the females don't know about the risk and symptoms of gestational diabetes [19]. In currents study it was mentioned that 101 (76.3%) don't have enough knowledge about management protocols. These findings are related to the study conducted by Ali RA *et al.*, in Egypt to evaluate the impact of self-care recommendations on pregnant women's knowledge and behavior regarding Gestational Diabetes Mellitus (GDM). Regarding the selfcare knowledge, only 4% of women had satisfactory knowledge about GDM and 95% had unsatisfactory practice. The study suggests ongoing health education initiatives and wider implementation of self-care recommendations to enhance knowledge and self-care behaviors related to GDM [20]. In a cross-sectional study carried out by Mahalakshmi B *et al.*, among 360 pregnant women in Tamil Nadu, India, 88%

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demonstrated awareness of Gestational Diabetes Mellitus (GDM). However, 60% of the participants were unaware that GDM could recur and 56% lacked knowledge about its treatment options. Understanding of Gestational Diabetes Mellitus (GDM) varies throughout the stages of pregnancy. Overall awareness, knowledge of dietary substitutes and management strategies tend to improve as the pregnancy advances through trimesters. The feeling of pregnant women to seek information also increases as their pregnancy progresses [21]. Self-care practices among women diagnosed with GDM can be shaped by various socio-demographic, physiological and psychosocial factors. Certain factors, such as maternal concerns regarding the health of their newborn and available social support, may aid in the management of GDM. Conversely, other factors, like physical and social limitations, as well as a lack of understanding about GDM management, can pose barriers to effective self-management [22].

CONCLUSIONS

The study suggests that most participants, have lack of knowledge of about GDM, moreover they have not adequate knowledge about the management of gestational diabetes mellitus (GDM), its symptoms and feto-maternal complications.

Authors Contribution

Conceptualization: SA[1]
Methodology: SA[1], NS, KA, HAI
Formal analysis: NS
Writing, review and editing: SA[2], HAI, MA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Association between Vitamin D Deficiency And Suicide Attempts In Patients With Major Depressive Disorder

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ABSTRACT

Major Depressive Disorder (MDD) is significant public health concern that is often associated with an increased risk of suicide attempts. Emerging research suggests that Vitamin D3, a nutrient primarily obtained through sunlight exposure and certain foods, plays a crucial role in brain health and mood regulation and thus affects various psychiatric disorders, including depression. **Objective:** To determine the association between decreased Vitamin-D levels and a history of attempted suicide among patients suffering from Major Depressive Disorder. **Methods:** A comparative cross-sectional study was carried out from December 2020 to June 2021, on a sample of 104 patients diagnosed with Major Depressive Disorder. Half of the samples were with Vitamin-D3 deficiency while half of the sample were without Vitamin-D3 deficiency. This research was carried out at the Department of Psychiatry and Behavioral Sciences, Liaquat University Hospital, Hyderabad, Pakistan. Data were analyzed with SPSS version 21.0. **Results:** The mean age of the sample stood at 44 years (09 ± SD). A majority of the sample comprised of male (55.77%), hailing from an urban background and a middle socioeconomic set-up (60.58%). The mean Vitamin-D level was 18.63 ng/ml, while the mean Vitamin-D3 level was 14.77 ng/ml and 22.05 ng/ml for groups A and B respectively. History of attempted suicide was more prevalent among patients with Vitamin D3 deficiency. **Conclusion:** The research concluded that Vitamin-D deficiency is found to be one of the factor for suicidal attempts in patients with Major Depressive Disorder.

INTRODUCTION

Suicide is a major leading social and public health issue worldwide, with an estimated global suicide death rate of 11/100,000 people (7/100,000 among female and 15/100,000 among male) [1]. In 2016, there were 817,000 suicide deaths globally, making up 1.5% of all deaths [2]. Suicide mostly affects young and middle-aged adults. It is the 2nd foremost reason of mortality among people with 15–29 years of age [3] and the 3rd foremost factor of mortality among people under 40 years of age [4]. In Pakistan, the rate of suicide in 2012 (according to World Health Organization estimates), stood at 7.5 out of every 100,000 people who died by suicide. In other words, around 13,000 people killed themselves that year. More recent statistics by WHO state that the condition is not getting much better and lives are continually being lost. Experts say the number of people dying is likely somewhere between the two figures i.e. 7/100,000 among female and 15/100,000 among male, but the exact situation remains elusive [5]. Official national rates of suicide in Pakistan are unavailable, are neither known nor included in the annual mortality statistics.

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Individual investigations have reported differing rates from a lower range of 0.43 per 100,000 per year in Peshawar to 2.86/100,000 per year for Rawalpindi. Other regions have same trend in the middle of the spectrum. Karachi has a suicide rate of 2.1/100,000, Lahore 1.08/100,000, Faisalabad 1.12/100,000, and Larkana 2.6/100,000 [6]. This suggests that some of the seasonality in suicide rates could be explained by exposure to certain risk factors for suicide in those seasons, since there is also a higher prevalence of suicide in locations with less sunlight [7] and during the holiday spring, when 25-hydroxy Vitamin-D [25(OH)D] levels are at their lowest. Skin exposure to UV-B is tightly linked with the synthesis of pre-Vitamin-D and subsequent levels of 25(OH)D [8], and high degree of seasonal variation in sunlight exposure leads to dramatic variations in amounts light hitting the skin throughout the year [8]. Many studies are bringing forth the beneficial effect of Vitamin-D on brain function. Mechanisms of Vitamin-D neuroprotection may also involve its neurotrophics activities, as it can regulate the transcription of more than 1,000 genes, including those which are related to a range of suicide-related processes [9]. The effects of hypertension on cognitive function and mood might be mediated, at least in part, by angiotensin II activity in adrenal glands, an action that may be induced by Vitamin-D effects (and prevented by anti VDR antibodies) on nuclear VDR present in many brain regions and which gene variations have been identified as associated with cognitive function and depressive symptoms [10, 11]. The causes of suicide are likely multifactorial, involving genetic, environmental, and psychological factors. Given the serious implications of attempted suicide, factors that are related to increased suicide attempts, even to a minute extent, merit exploration so that the appropriate preventive and therapeutic measures can be ensured to decrease the burden. The matter becomes even more important given that there is a high level of Vitamin-D deficiency among all age groups, genders, income levels, and regions in Pakistan (expected to be 53.5% in general population)[11].

The aim of this study was to determine the association between decreased Vitamin-D levels and history of attempted suicide among patients suffering from depression.

METHODS

A comparative cross-sectional study was carried out from December 2020 to June 2021, on 104 individuals of either gender with age range 18-65 years and diagnosed with Major Depressive Disorder. Patients were chosen via non-probability consecutive sampling. Patients with bipolar depression, schizophrenia, obsessive compulsive disorder, and with or without comorbid substance abuse of any illicit drug (as described by DSM-5) and those suffering from major systematic diseases like diabetes mellitus, hypothyroidism, hyperthyroidism, arthritis, etc. were excluded from the study. This research was done at the Department of Psychiatry and Behavioral Sciences, Liaquat University Hospital, Hyderabad, Pakistan. The study was approved by the Research Ethics Committee of Liaquat University of Medical and Health Sciences (IRB-LUMHS/REC/984, Dated; 06/12/2020). Sample size was calculated by using an Open-Epi sample size calculator, by taking the incidence of Vitamin-D3 deficiency in depressed patients with (58%) and without (29%) history of attempted suicide [12], with confidence interval of 95% and power of study as 80%. An informed written consent was obtained from each participant prior to enrollment in the study. An anonymous self-structured questionnaire containing inquiries about the basic biodata, sociodemographic details and details about the history of suicide attempt was used. The Hamilton Depression Rating Scale, Beck's Suicidal Ideation Scale, and Beck's Suicidal Intent Scale were used for the assessment of the severity of depression, suicidal ideation, and intent. The Hamilton Depression Rating Scale (HDRS) was used to evaluate depression severity in patients, consisting of 17 items assessing symptoms like mood, guilt, insomnia, agitation, anxiety, and weight loss. The Beck's Suicidal Ideation Scale (BSIS), a 19-item self-report inventory, measured the frequency, intensity, and duration of suicidal thoughts, identifying individuals at risk of suicide. The Beck's Suicidal Intent Scale (BSIS) assessed the seriousness of suicidal intent through 15 items evaluating the degree of planning and likelihood of rescue. 10 ml venous blood samples of all enrolled participants were collected and sent to the pathology laboratory, to screen for Vitamin-D3 deficiency. Decreased Vitamin-D3 was defined as total serum Vitamin-D3, of less than 20 ng/ml. The patients were divided into 2 groups (A: MDD with Vitamin-D3 deficiency and B: MDD without Vitamin-D3 deficiency) of 52 each and inquired about a history of attempted suicide. Data were analyzed using SPSS version 21.0. Chi-Square test was applied to compare the incidence of suicidal attempts among low and high Vitamin-D3 level patients.

RESULTS

The mean age of participants in Group A with Vitamin-D deficiency was 43 years, while in Group B those without Vitamin-D deficiency, it was 45 years, showing no significant difference between the groups. In terms of gender distribution, Group A had 37 male (71.2%) and 15 female (28.8%), whereas Group B had 21 male (40.4%) and 31 female (59.6%), with a statistically significant difference observed ($p < 0.05$). Regarding residential status, 38 participants (73.1%) in Group A resided in urban areas, compared to 34 (65.4%) in Group B, with no significant

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difference noted ($p > 0.05$). In socioeconomic status, Group A had 21 participants (40.4%) classified as lower, 30 (57.7%) as middle, and 1 (1.9%) as upper, while Group B had 10 (19.2%) lower, 33 (63.5%) middle, and 9 (17.3%) dupper, indicating a significant difference in the lower and upper categories ($p < 0.05$) (Table 1).

Table 1: Descriptive Statistics (Group-Wise Comparison)

Variable	Group A (With Vitamin D Deficiency)	Group B (Without Vitamin D Deficiency)	p-Value
Mean Age (Years)	43	45	> 0.05
Gender			
Male	37 (71.2%)	21 (40.4%)	< 0.05
Female	15 (28.8%)	31 (59.6%)	
Residential Status			
Urban	38 (73.1%)	34 (65.4%)	< 0.05
Rural	14 (26.9%)	18 (34.6%)	
Socioeconomic Status			
Lower	21 (40.4%)	10 (19.2%)	< 0.05
Middle	30 (57.7%)	33 (63.5%)	
Upper	1 (1.9%)	9 (17.3%)	

There were no significant differences in the history of attempted suicide when comparing Vitamin-D status with depression and suicide in Group A (Vitamin-D deficiency) and Group B (Without Vitamin D deficiency) ($p > 0.05$). The Hamilton Depression Rating Scale assessed depression severity, significant differences were found in the mild to moderate ($p < 0.05$) and moderate to severe ($p < 0.05$) categories (Table 2).

Table 2: Vitamin-D Status versus Depression and Suicide

Variable	Group A (With Vitamin D Deficiency)	Group B (Without Vitamin D Deficiency)	p-Value
History Of Attempted Suicide			
Present	9 (17.3%)	6 (11.5%)	< 0.05
Absent	43 (82.7%)	46 (88.5%)	
Hamilton Depression Rating Scale Score			
Mild	14 (26.9%)	11 (21.2%)	< 0.05
Mild To Moderate	32 (61.5%)	19 (36.5%)	
Moderate To Severe	18 (34.6%)	10 (19.2%)	
Becks Suicidal Ideation Scale Score			
Suicidal Ideation Present	28 (53.9%)	25 (48.1%)	< 0.05
Suicidal Ideation Absent	24 (46.1%)	27 (51.9%)	
Hamilton Depression Rating Scale Score			
Suicidal Intent Present	51 (98.1%)	49 (94.2%)	< 0.05
Suicidal Intent Absent	01 (1.9%)	03 (5.8%)	

Examining the relationship between attempted suicide and demographic features revealed no significant differences in gender, residential status, or socioeconomic status between those who had attempted suicide and those who had not ($p > 0.05$). In both gender and residential status categories, the proportion of participants who attempted suicide was similar across subgroups. However, in the socioeconomic status category, a notable difference was observed, with 50% of participants in the upper category reporting attempted suicide (Table 3).

Table 3: Attempted Suicide versus Demographic Features

Variable	Attempted Suicide		p-Value
	Present	Absent	
Gender			
Male	8 (13.8%)	50 (86.2%)	< 0.05
Female	7 (15.2%)	39 (84.8%)	
Residential Status			
Urban	9 (12.5%)	63 (87.5%)	< 0.05
Rural	6 (18.8%)	26 (81.2%)	
Socioeconomic Status			
Lower	4 (12.9%)	27 (87.1%)	< 0.05
Middle	6 (9.5%)	57 (90.5%)	
Upper	5 (50.0%)	5 (50.0%)	

DISCUSSION

The research suggests that low Vitamin-D levels may be linked to suicide attempts in depressed patients, though our findings weren't statistically significant. Our results are consistent with several previous studies that found lower Vitamin-D levels associated with a higher risk of depression [13-15]. Most of these studies focused on older adults. For example, Desai et al. [16] found in the Longitudinal Aging Study Amsterdam that depression symptoms, measured by the CES-D score, were significantly connected to 25(OH)D3 levels. People with major and minor depression had 14% lower 25(OH)D3 levels than those without depression. Milaneschi et al. conducted a six-year study attempting to analyze both social support sources and the quantity of emotional support on depression development published in 2014. Survival analyses showed that women with low Vitamin-D levels were much more likely to develop a depressed mood (p value=0.005) [17]. In contrast, Jeenduang and colleague reported furnished basolateral membrane-associated ATL3 localization, showing there is no relationship between Vitamin-D levels and depression [18]. The discrepancies between our study and those by Desai and Milaneschi [16-17] are associated with our small sample size, resulting in inadequate statistical power. Prior research has identified multiple potential biological mechanisms underlying the association between Vitamin-D levels and depression. In the same way, may Vitamin-D deficiency perturb the neuroendocrine and central nervous systems in terms of the regulation of neurotransmission, neuroprotection, neuroimmunomodulation, and release of cortisol and neurotransmitters [19, 20]. The average age of the participants was 44 years (09 ± SD), with the sample predominantly composed of males (55.77%), mainly from urban areas and middle socioeconomic backgrounds

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(60.58%). The average Vitamin-D level among the participants was 18.63 ng/ml, with group-wise mean Vitamin-D3 levels of 14.77 ng/ml for group A and 22.05 ng/ml for group B. Vitamin-D insufficiency and deficiency are global concerns impacting individuals of all ages and races. Optimal skeletal health requires 25(OH) Vitamin-D levels above 30 ng/ml. Typically, serum 25(OH) Vitamin-D levels are lower in Black individuals compared to White individuals, and in those who avoid sun exposure. Among older adults in the US and Europe, Vitamin-D deficiency prevalence ranges from 40% to 100%. Bertone-Johnson et al, found that around 25% of men over 50 and 30-35% of women over 50 had 25(OH) Vitamin-D levels below 0.001 [21]. Various studies indicate that Vitamin D deficiency at its binding sites can lead to mood disorders, both major and minor. These studies demonstrate that treatments such as Vitamin D or sunlight therapy (phototherapy), Gene Therapy, or a Vitamin D-supplemented diet can effectively treat depression and other mood disorders. They also reveal a correlation between 25(OH) Vitamin D levels and mood, as well as mood and cognition, across all age groups, including pregnant women, older adults, and Vitamin D deficient populations worldwide [22]. Additionally, plasma Vitamin D levels appear to influence mood and cognitive performance to some extent [23]. Improvements in depression scales were observed with Vitamin-D supplementation, though less so with phototherapy. It is recommended to take at least 800 IU of Vitamin D daily, as this dosage is crucial in studies on mood disorders [24, 25]. A history of attempted suicide was more common among patients with Vitamin-D3 deficiency, although this difference was not statistically significant. Evidence indicates significantly lower Vitamin-D levels in individuals with suicidal tendencies compared to controls. Literature suggests that Vitamin-D deficiency was found in 58% of reported suicide cases, compared to about 30% in healthy controls and non-suicidal depressed patients [26-28].

CONCLUSIONS

The study concluded that the Vitamin-D deficiency is found to be one of the factor for suicidal attempts in patients with Major Depressive Disorder. Awareness and education regarding this association to mental health professionals is recommended to lessen the burden of attempted suicide.

Authors Contribution

Conceptualization: ZAM
Methodology: SA, ASL, HS
Formal analysis: ZAM, SA, AGA, SB
Writing-review and editing: SA, ASL, AGA, SB, HS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Frequency of Thyrotoxicosis in Patients Presenting with Unilateral Proptosis in District Headquarters Teaching Hospital D.I.Khan

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ABSTRACT

Thyrotoxicosis is a medical disorder marked by retraction of the eyelids, resulting in a wide-eyed or gazing appearance. This syndrome can occur in patients with any form of hyperthyroidism as a result of increased activity of the sympathetic nervous system. **Objectives:** To investigate the prevalence of thyrotoxicosis and factors contributing to unilateral proptosis, with a specific focus on early diagnosis and prompt treatment. **Methods:** A cross-sectional study was conducted from January 2023 to January 2024 and categorical variables were presented with the frequency and percentage. The study had a total of 62 patients who exhibited unilateral proptosis. The clinical examinations involved a comprehensive collection of medical history, examination of eyes, analysis of blood samples, evaluation of thyroid function, and utilization of advanced imaging techniques. The associations between thyrotoxicosis and demographic variables were evaluated using chi-square tests. Data were entered and analyzed on SPSS version 26. **Results:** The mean age of participants was 27.84 ± 6.8 years and female comprised 54.8% of the total. It was observed that female had a greater incidence rate (73.5%) compared to male (53.6%) ($p>0.05$). Additional findings included retrobulbar tumors (16.1%), cavernous sinus thrombosis (12.9%), and idiopathic proptosis (6.5%). The prevalence of thyrotoxicosis was highest among individuals aged 15-30 ($p<0.05$). The most common symptom linked with thyrotoxicosis was diplopia (33.9%) ($p<0.05$). **Conclusions:** Thyrotoxicosis has a major role in causing unilateral proptosis, especially in female and younger persons. Being female and experiencing pain may serve as predictors for thyrotoxicosis.

INTRODUCTION

Thyroid Eye illness (TED), commonly referred to as Graves' Ophthalmopathy, is acknowledged as the most common non-thyroidal symptom of Graves' illness [1, 2]. This condition is mainly characterized by the enlargement of the tissues around the eye socket, which includes the expansion of connective and fatty tissues, as well as the growth of extraocular muscles in the spaces between these tissues [3]. These alterations take place inside the limited area of the bony orbit, frequently causing an immunological response that progresses autonomously, culminating in tissue hypoxia, damage caused by oxygen free radicals and remodeling of fibrous tissue [4-6]. TED often advances through two stages: an initial phase of active inflammation that normally lasts between 6 to 24 months (sometimes longer), followed by a static phase [7]. Exophthalmos, also known as proptosis, is a prominent symptom that can be noticed in 20-30% of people with Graves' disease and up to 40-70% of patients with TED. Pure unilateral ophthalmopathy, where only one eye is damaged, is a rare occurrence, accounting for about 5-11%

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of cases [8-10]. The occurrence of TED, specifically exophthalmos, differs among different populations. European people bear significantly high prevalence of Graves' Ophthalmopathy compared to Asians. The rate among Europeans is 42%, whereas among Asians is 7.7% [11, 12]. Moreover, Europeans are 6.4 times more prone to develop the Graves' Ophthalmopathy than Asians [11]. TED is a primary reason for both one-sided and two-sided bulging of eyes, impacting about half of individuals with Graves' disease. Approximately 5% of these patients have potential to develop severe dysthyroid optic neuropathy [13]. Additional possible factors contributing to proptosis include orbital cellulitis, mucormycosis, retroorbital tumors and cavernous sinus thrombosis [14]. The cure for TED involves utilizing immunosuppressive drugs when the disease is active and surgical procedures when disease is quiescent. For certain patients, rehabilitative surgical operations including orbital decompression and eyelid surgery is required when the disease becomes stable [15].
The objective of the study was to evaluate the frequency of thyrotoxicosis and other factors contributing to unilateral proptosis, specifically focusing on treatable underlying causes for improving the identification and treatment of unilateral proptosis caused by thyrotoxicosis.

METHODS

A cross-sectional investigation was conducted at the Department of Ophthalmology, District Headquarters Teaching Hospital, Dera Ismail Khan, from January 2023 to January 2024, to evaluate the frequency of thyrotoxicosis and other potential reasons for unilateral proptosis. Prior to their involvement, informed consent was acquired from each patient. The study adhered to the ethical principles specified in the Declaration of Helsinki and obtained permission from Gomal Medical College, Dera Ismail Khan, Pakistan (IRB-273/GJMS/JC, Dated; December 26, 2022). The study included 62 participants having unilateral proptosis. The inclusion criteria comprised the patients exhibiting unilateral proptosis caused by orbital causes. The exclusion criteria comprised unilateral ocular disorders, such as extreme myopia or congenital glaucoma. Each participant underwent a detailed medical history assessment, which included gathering information about the length of the disease, the way it started and course of symptoms over time. In addition any accompanying symptoms such as diplopia, fever, discomfort and visual loss were noted down. An extensive ophthalmological examination was performed, that included evaluation of the orbit, eyelid, front and back parts of the eyes. Comprehensive health evaluations involve assessing thyroid function, conducting a complete blood count (CBC) and analyzing other pertinent blood indicators. These tests were conducted to identify any anatomical abnormalities including routine imaging investigations such as X-rays of orbit, skull and sinuses. Advanced imaging techniques such as magnetic resonance imaging (MRI), dye-contrast orbitography, internal carotid arteriography, orbital tomography and specialized views of optic foramina were used to get to determine the causes of proptosis. Thyroid function tests (TFTs), including measurements of thyroid-stimulating hormone (TSH) as well as levels of thyroid hormones (free T3 and free T4), were employed to assess for the presence of thyrotoxicosis. The histopathological investigation was used to confirm the diagnosis of suspicious neoplasms. The collected data were examined to determine the frequency of thyrotoxicosis and other factors that contribute to unilateral proptosis. The statistical analyses were conducted using SPSS version 26.0 software, applying descriptive statistics to summarize patient demographics, clinical results and diagnostic outcomes. The associations between the presence of thyrotoxicosis and demographic variables were assessed using chi-square tests.
The sample size for this study was determined based on the expected prevalence of unilateral proptosis caused by thyrotoxicosis or other factors, along with a margin of error and confidence level. Given an expected prevalence of 10%, a confidence level of 95%, and available resources, the researchers aimed to achieve a balance between precision and feasibility. The sample size was calculated using the formula.

$$d^2=z^2\cdot p\cdot(1-p)/n$$

Where;
z is the z-value for a 95% confidence level (1.96), p is the expected prevalence (10%) and *n* is the sample size. This margin of error (7.5%) was considered acceptable given the practical constraints and the study's aims, leading to a final sample size of 62 participants.

RESULTS

An in-depth analysis of the demographic characteristics of patients with unilateral proptosis revealed their mean age as 27.84 ± 6.8 years, with a range of 15-60 years. A younger age prevalence was shown by the fact that 67.7% of patients fell between the ages of 15 and 30. The female population constitutes 54.8% of the total, while the male population made 45.2%. Additional symptoms included double vision (33.9%), discomfort (14.5%), elevated body temperature (11.3%) and decreased visual acuity (4.8%) ($p>0.05$) (Table 1).

Table 1: Detailed Demographics of Patients with Unilateral Proptosis

Parameter	n (%)
Age (Years)	
Mean ± SD	27.84 ± 6.8
Range	15-60 Years

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Age Groups	
15-30	42 (67.7)
31-45	12 (19.4)
46-60	8 (12.9)
Gender	
Male	28 (45.2)
Female	34 (54.8)
Associated Symptoms	
Diplopia	21 (33.9)
Pain	9 (14.5)
Fever	7 (11.3)
Vision Loss	3 (4.8)

The incidence of thyrotoxicosis was higher in female (73.5%) compared to male (53.6%). But there was no statistically significant relationship between sex and incidence of thyrotoxicosis ($p>0.05$) (Figure 1).

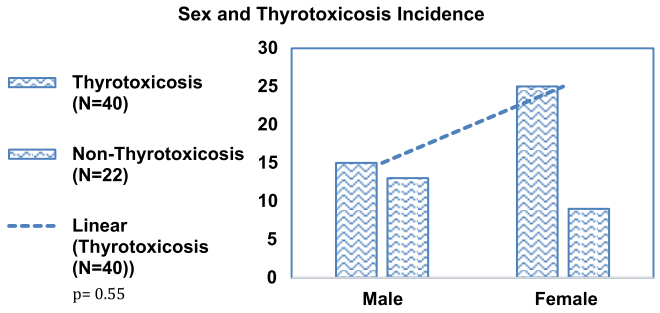

Figure 1: Association between Sex and Thyrotoxicosis Incidence

The distribution of etiologies by age group showed that thyrotoxicosis was most commonly found in 15-30 age range, with a prevalence rate of 62.5%. Retrobulbar tumors exhibit a reasonably uniform distribution across different age groups, but cavernous sinus thrombosis was most commonly observed in individuals aged 31-45, accounting for 50% of cases. Idiopathic proptosis was seen in individuals of all age groups, however it was slightly more prevalent in younger individuals ($p<0.05$) (Table 2).

Table 2: Distribution of Etiologies by Age Group

Age Group (Years)	Thyrotoxicosis (n=40)	Retrobulbar Tumor (n=10)	Cavernous Sinus Thrombosis (n=8)	Idiopathic Proptosis (n=4)	Chi-Square	p-Value
15-30	25 (62.5)	4 (40.0)	2 (25.0)	2 (50.0)	5.67	0.046*
31-45	11 (27.5)	3 (30.0)	4 (50.0)	1 (25.0)		
46-60	4 (10.0)	3 (30.0)	2 (25.0)	1 (25.0)		

The correlation between sex and several causes of proptosis was also examined. Thyrotoxicosis had higher prevalence in female (73.5%) compared to the male (53.6%). The frequency of retrobulbar tumors, cavernous sinus thrombosis, and idiopathic proptosis were similar in both male and female, indicating non-significant relationship between sex and various proptosis etiologies (Table 3).

Table 3: Association between Gender and Different Proptosis Etiologies

Etiologies	Male (n=28)	Female (n=34)	Total (n=62)	Chi-Square	p-Value
Thyrotoxicosis	15 (53.6)	25 (73.5)	40 (64.5)	2.87	0.41
Retrobulbar Tumor	5 (17.9)	5 (14.7)	10 (16.1)		
Cavernous Sinus Thrombosis	5 (17.9)	3 (8.8)	8 (12.9)		
Idiopathic Proptosis	3 (10.7)	1 (2.9)	4 (6.5)		

The prevalence of thyrotoxicosis was higher in the younger age group (15-30 years), with an incidence rate of 62.5%. The occurrence was less frequent in older age groups, indicating a decrease in frequency as age increases ($p<0.05$), suggesting that age did not play a large role in determining the occurrence of thyrotoxicosis (Table 4).

Table 4: Incidence of Thyrotoxicosis in Various Age Groups

Age Group (Years)	Male (n=15)	Female (n=25)	Total (n=40)	Chi-Square	p-Value
15-30	10 (66.7)	15 (60.0)	25 (62.5)	3.22	0.05*
31-45	3 (20.0)	8 (32.0)	11 (27.5)		
46-60	2 (13.3)	2 (8.0)	4 (10.0)		

Thyrotoxicosis was linked to the greatest percentage of diplopia (45.0%), discomfort (17.5%) and fever (10.0%). Other causes exhibited lesser frequency of symptoms, whereas idiopathic proptosis did not present any accompanying symptoms. It also suggested that there was no statistically significant difference in the distribution of symptoms among distinct causes ($p<0.05$) (Table 5).

Table 5: Associated Symptoms by Etiology

Etiologies	Diplopia	Pain	Fever	Vision Loss	Chi-Square	p-Value
Thyrotoxicosis (n=40)	18 (45.0)	7 (17.5)	4 (10.0)	2 (5.0)	4.12	0.028*
Retrobulbar Tumor (n=10)	2 (20.0)	1 (10.0)	1 (10.0)	0 (0.0)		
Cavernous Sinus Thrombosis (n=8)	1 (12.5)	1 (12.5)	1 (12.5)	1 (12.5)		
Idiopathic Proptosis (n=4)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)		

DISCUSSION

The main objective of the study was to assess the frequency of thyrotoxicosis in patients who had unilateral proptosis. Our findings indicated that the disorder primarily affected female and people in younger age brackets. The study findings indicated that thyrotoxicosis was the predominant underlying cause [16]. The high occurrence of this condition emphasized the importance of considering thyrotoxicosis as a significant potential cause of unilateral proptosis. The predominance of female affected by thyroid eye illness, as observed in our study, corresponded with worldwide patterns. Multiple studies [16-19] consistently indicated a higher prevalence of the disease in female compared to male. Within our dataset, the proportion of female patients was 54.8%, which supported this observation. The statistics also showed a mean patient age

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of 27.84 years, which aligned with the results of prior studies. For example, Zarei *et al.*, [19] found that the average age was 34 ± 12.0 years, but Khan *et al.*, [20] observed a significantly higher average age of 44.8 ± 12.4 years. In our investigation, retrobulbar tumors were found responsible for 16.1% of cases with unilateral proptosis, in addition to the high occurrence of thyrotoxicosis. Cavernous sinus thrombosis, characterized by the formation of blood clots in the cavernous sinus located at the base of the brain, was observed in 10.6% of cases. This issue can lead to serious eye difficulties and needs to be quickly identified and treated. A tiny percentage of instances exhibited idiopathic proptosis, however, it is important to evaluate the presence of small masses, cysts, and reactive hyperplasia in cases where the cause of proptosis is not immediately apparent. Therefore, it is recommended to perform MRI imaging of the brain and orbit in all cases with unilateral proptosis to thoroughly investigate potential reasons. The incidence rate of thyrotoxicosis was considerably higher in the younger age group (15-30 years). This implied that thyrotoxicosis is more likely to develop in younger individuals as a cause of unilateral proptosis than in older age groups. The lower incidence in older age groups suggested that age is a significant factor in the development of thyrotoxicosis [20-24]. Among the etiologies examined, thyrotoxicosis was associated with the highest percentage of diplopia, distress, and fever. These symptoms were significantly associated with thyrotoxicosis, emphasizing the significance of taking these clinical presentations into account when diagnosing thyrotoxicosis in patients with proptosis. The necessity of comprehensive clinical evaluations, which include detailed symptom assessments, to guarantee accurate diagnosis and expeditious treatment is underscored by the substantial correlation between these symptoms and thyrotoxicosis [25]. Exophthalmos (protrusion of eyeballs) is a frequently observed sign of this eye disease. It is most common during the initial year of the disease's onset. During the second year, occurrence of thyrotoxic goiter became more common, affecting around 60 to 80% of cases [26]. Nevertheless, the extent of exophthalmos may not exhibit a direct correlation with the intensity of thyrotoxicosis, since substantial protrusion can occur even in the presence of relatively minor thyroid symptoms [27]. Macovei observed that a small proportion of individuals with exophthalmic goiter exhibited a reduced basal metabolic rate, typically falling within the range of plus 10 to plus 20% [28]. Exophthalmos may occur before other clinical indications of thyrotoxicosis in exceptionally uncommon instances. There are only a few studies in the literature that describe this phenomenon, with eight reported occurrences where exophthalmos appeared prior to any indications of thyrotoxicosis. Nevertheless, even in these instances, the reliability of certain accounts seems uncertain [29]. Thyrotropic exophthalmos, which is caused by excessive release of thyrotropic hormone from the pituitary gland, can develop when there is an excess of male hormones and insufficient levels of thyroxine. The significance of doing a comprehensive endocrine evaluation in the diagnosis and treatment of unilateral proptosis is emphasized by this condition [30]. The significant findings of this study provided valuable insights into the characteristics and potential predictors of thyrotoxicosis. Furthermore, the etiology of unilateral proptosis could be further clarified by investigating supplementary factors, including genetic predispositions and environmental influences.

CONCLUSIONS

Thyrotoxicosis was identified as the primary cause of unilateral proptosis, particularly affecting young women. We recommend comprehensive evaluation for thyrotoxicosis in all proptosis cases, including thyroid function tests and MRI to rule out other etiologies. The significant association with symptoms such as diplopia, discomfort, and fever underscores the need for thorough clinical assessment to ensure accurate diagnosis and prompt treatment.

Authors Contribution

Conceptualization: SK, NUR
Methodology: SK, AR
Formal analysis: AR, RN
Writing-review and editing: SK, NUR, AR

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Frequency of Zygomatic Complex Fracture in Patients Presenting to Ayub Teaching Hospital

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ABSTRACT

Zygomatic complex fractures are a prevalent type of facial injury. It often results from road traffic accidents (RTA). It poses significant clinical challenges. **Objective:** To find out the frequency of zygomatic complex fractures among patients introduced at the Ayub Teaching Hospital. **Methods:** This cross-sectional study was carried out in the Department of Oral and Maxillofacial Surgery at Ayub Teaching Hospital, Abbottabad, Pakistan after approval from IRB (Institutional Review Board) of the Ayub Teaching Hospital Abbottabad, (IRB-F5/Dent/AMC&ATH) from September 1, 2019, to March 1, 2020. A total of 146 patients, including both genders and revealing oral and maxillofacial injury, were essential parts of the research. Before performing meticulous intra and extra-oral clinical examinations and computed tomography (CT) scans in the Department of Radiology to diagnose zygomatic complex fractures. **Results:** Out of the total number of 146 patients, 33.6% had ZMC fractures. The study involved patients aged 18-60 years. This is consistent with an average age of 31.993 ± 8.00 years and a mean weight of 74.664 ± 9.26 kg. Male patients represented 74.7% of cases and female comprised 25.3%. The primary causes of fractures were road traffic accidents, falls, and sports injuries. **Conclusions:** The research concluded that zygomatic complex fractures occurred due to road traffic accidents (RTA), which are more common in this region. Thus, the examination highlights the basic requirement for procedures to alleviate street mishaps to abridge such terrible facial injuries.

INTRODUCTION

The prominence and structural significance of the zygomatic bone are well known, which is connected with the temporal, sphenoid, frontal, and maxillary bones to form the lateral and anterior regions of the face. It also protects the contents of the orbit. Notably, fractures influencing the zygomatic complex stand among the most predominant injuries in facial injury, especially pervasive in grown-up adults [1]. Pattern and severity of fracture associated with causative factor, magnitude of factor, duration of impact, and other etiological factors [2, 3]. These fractures have many different causes, including sports-related incidents, assaults, falls, and road accidents [4]. In any case, the epidemiology of maxillofacial fractures shows topographical and sociodemographic variability, affected by social, financial, and surrounding factors [5]. Fractures of the alveolar process are frequently observed in 2-8% of all craniofacial injuries. It was also seen that the severity of damage increased with soft tissues and teeth [6]. Frequently fractures occur due to motor vehicle accidents, playground accidents, falls, and sports injuries [7]. Moreover, direct or indirect pressure on a tooth may lead to overlying the soft

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tissues which further cause the dentoalveolar injury [8]. Approximately, 1-8% of pediatric fractures occurred due to midfacial fractures, which are less common among children and may affect the mandible bone [9]. The low proportion may be due to the mandible and cranium bone providing protection, which act like absorbent and absorb most traumatic impacts due to the flexibility of osseous suture lines and the elasticity nature of midfacial bones [10]. The number of children with fractures of midfacial bones is increasing with the passage of time, which might be due to the usage of suitable imaging modalities [11]. Clinical signs of zygomatic complex fracture include diplopia, enophthalmos, subconjunctival ecchymosis, capture of extraocular muscles, malar eminence depression, facial extending, malocclusion, and infraorbital nerve-related neurosensory instabilities [12, 13]. Clinical examination is the primary method of diagnosis, which is typically supported by computed tomography (CT) scans [14]. Early and exact diagnosis stays crucial for ideal treatment, highlighting the significance of exact injury evaluation and timely treatment providences [15]. Surgical management is the primary choice of treatment for displaced zygomatic complex fractures, apart from cases in which surgery is contraindicated due to the medical health of the patient or denied by the patient because of aesthetic concerns [16]. The surgical treatment of fractured zygomatic complexes is the subject of extensive research in the existing literature [17]. Research like the ones carried out by Khan *et al.*, showing a 27% recurrence of zygomatic complex fractures [18], and Tripathi *et al.*, detailing a recurrence of 41.48% [19], further highlight the frequency of these injuries. A larger part of the mid-third of facial fractures include the zygomatic complex, however, the rate varies across different population. The exact treatment and management of zygomatic complex fractures turn on a careful pattern of fractures within one specific group of people. As a feature of this undertaking, this study means to find out the recurrence of zygomatic complex fractures among patients owned up to the ER [20]. The final results of this research are expected to contribute vital proof in regards to this subject among our population, possibly molding more designated and compelling ways to manage these fractures.

This study aimed to find the frequency of zygomatic complex fractures among patients introduced at the Ayub Teaching Hospital.

METHODS

A cross-sectional study was conducted from September 1, 2019, to March 1, 2020, in the Department of Maxillofacial Surgery at Ayub Teaching Hospital, Abbottabad, Pakistan after approval from IRB (Institutional Review Board) of the Ayub Teaching Hospital Abbottabad, (IRB-F5/Dent/AMC&ATH). The Sample comprised 146 patients. Certainty level of 95%, an expected extent of zygomatic complex fractures in patients with maxillofacial injury of 41.48%, and an absolute accuracy of 8%. For participant selection, non-probability consecutive sampling was used [20]. Individuals between the ages of 18 and 60, regardless of gender, who presented to the emergency department with a history of oral and maxillofacial trauma were included in the inclusion criteria. Fractures caused by gunshot wounds and people who refused informed consent were added to the exclusion criteria. After obtaining written approval and endorsement from the ethical council. After obtaining their informed consent, eligible patients who presented with oral and maxillofacial trauma at the Maxillofacial Surgery Emergency Department, Ayub Teaching Hospital, Abbottabad, were enrolled. Patient qualities like age, orientation, weight (estimated on a weighing scale), and the reason for injury were recorded using a standardized data collection form. Comprehensive intra- and extra-oral clinical examinations and detailed histories were obtained. Patients went through CT checks and the identification of zygomatic complex fractures adhered to the researcher's standardized definition. Data analysis was performed utilizing IBM-SPSS-rendition version 22.0. Quantitative variables like age and weight were shown as Mean ± SD, whereas categorical variables like gender, trauma cause, and the incidence of zygomatic complex fractures were shown as frequency and percentage. Separation was completed in view old enough, orientation, weight, and justification behind injury to evaluate their effect on zygomatic complex break event. Post-definition chi-square tests were applied, and measurable importance was set at $p \leq 0.05$.

RESULTS

The participants in the study ranged in age from 18 to 60, with a mean age of 31.99 ± 8.00 years and a weight of 74.66 ± 9.26 kilograms. Approximately 75% of the patients were male and approximately 25% were female (Figure 1).

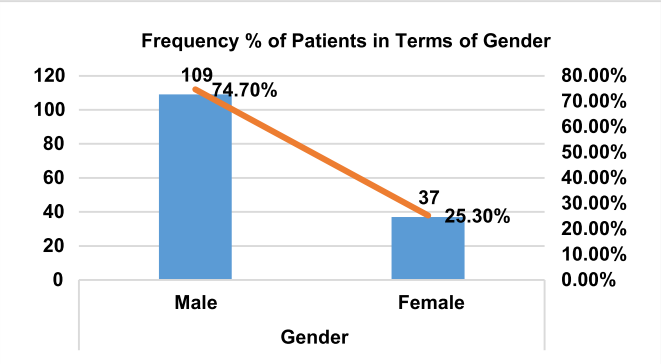

Figure 1: Frequency and Percentage of Patients in Terms of Gender at Ayub Teaching Hospital

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The patients had various reasons for injury among which 75% were the cases of road traffic accidents, 31% were violent assaults, 33% had fall history and 7% were related to sports injuries (Figure 2).

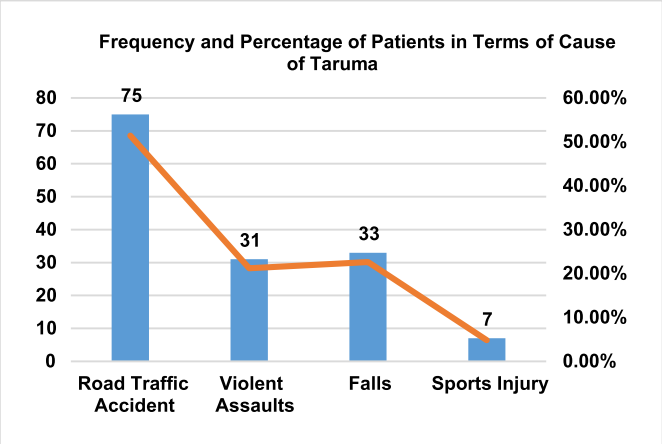

Figure 2: Frequency and Percentage of Patients in Terms of Cause of Trauma at Ayub Teaching Hospital (Total Traumatic Cases=146)

Among the total trauma cases i.e. 146 patients, 33.6% had ZMC fracture and 66.4% were the cases not involving the ZMC fracture (Figure 3).

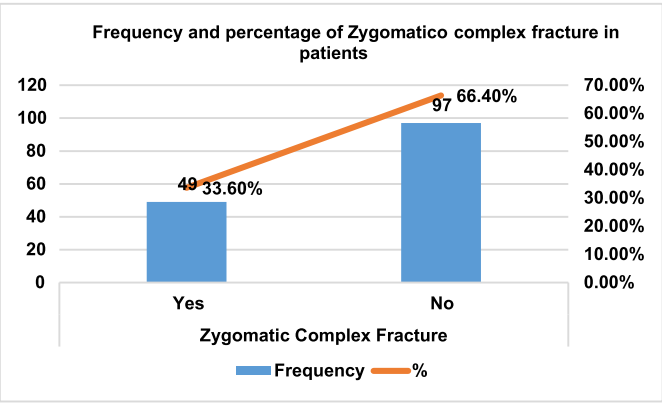

Figure 3: Frequency and Percentage of Zygomatic Complex Fractures in Patients at Ayub Teaching Hospital (49 Out of 146 are ZMC Fractures)

All the data mentioned in the above figures summarized in the table below which show the frequency of patients in terms of gender, cause of trauma, and ZMC fracture (Table 1).

Table 1: Frequency % of Patients in Terms of Gender, Cause of Trauma and Zygomatic Complex Fracture (n=146)

Variables		Frequency %
Gender	Male	109 (74.7%)
	Female	37 (25.3%)
	Total	146 (100%)
Cause of Trauma	Road Traffic Accident	75 (51.4%)
	Violent Assaults	31 (21.2%)
	Falls	33 (22.6%)
	Sports Injury	7 (4.8%)
	Total	146 (100%)
Zygomatic Complex Fracture	Yes	49 (33.6%)
	No	97 (66.4%)

Zygomatic complex fractures were dispersed among various age gatherings, sex, loads, and purposes behind the injury (Table 2).

Table 2: Division of Zygomatic Complex Fracture in Terms of Age, Gender, Weight, and Cause of Trauma

Variables		Zygomatic Complex Fracture		p-value
		Yes	No	
Age (Years)	18-40	41 (33.1%)	83 (66.9%)	0.763
	41-60	8 (36.4%)	14 (63.6%)	
Gender	Male	39 (35.8%)	70 (64.2%)	0.330
	Female	10 (27%)	27 (73%)	
Weight (kg)	≤80	35 (32.1%)	74 (67.9%)	0.524
	>80	14 (37.8%)	23 (62.2%)	
Cause of Trauma	Road Traffic Accident	33 (44%)	42 (56%)	0.009
	Violent Assaults	3 (9.7%)	28 (90.3%)	
	Falls	11 (33.3%)	22 (67.7%)	
	Sports Injury	2 (28.6%)	5 (71.4%)	

DISCUSSION

The prevalence, demographics, etiology, and treatment of zygomatic bone fractures, particularly facial fractures, are the primary topics of discussion in this article. It features that zygomatic bone fractures, comprising the most well-known among facial fractures, overwhelmingly influence people within a particular age group and gender, primarily happening because of different mishaps like industrial mishaps, sports injuries, and road traffic accidents. Zygomatic bone fractures, framing the anterolateral projection of the center face, address a huge part of facial fractures. This thesis article dives into the socioeconomics, causative factors, and helpful treatment modalities concerning these fractures. Studies show a majority event of zygomaticomaxillary complex (ZMC) fractures among people aged 18 to 41, affecting a greater population of male gender (74.7%) [21]. This gender incline lines up with worldwide patterns seen in comparable studies, credited to higher male contribution in exercises inclined to injury, for example, road traffic accidents, falls, and sports injuries. This study mirrors discoveries in different areas, highlighting the effect on young adults participating in ventures [22, 23]. Etiologies for zygomaticomaxillary complex cracks show territorial inconsistencies. While created nations witness a decrease in road traffic accidents, this review, directed in Abbottabad, recognized road traffic accidents as the primary causative factor (44%) [23]. Contrasting sociocultural settings, for example, lack of safety measures, essential education about road sense in common people, and low financial conditions, contribute essentially to this pattern in the neighborhood people. In

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contrast, alcohol abuse and social dissatisfaction lead to assault-related injuries in other regions [24]. This study aligns with the findings of Shah *et al.,* who reported a similar male predominance in facial fractures. He found a predominance of zygomatic complex fractures in males (74.7%). This gender predominance indicates the involvement of male in activities prone to injuries [2]. These injuries include road traffic accidents and sports. Additionally, our studies were supported by the work of Liu *et al*. [1]. He reported comparable age and gender distributions in their study on facial fractures. These fractures were caused by falls. It also supports our demographic findings. Our study showed that RTA (44%) was the leading cause of ZMC fracture. It is not the common cause of ZMC fracture in developed nations. These results were consistent with the findings of as described by Dikhit and Gaggl [25, 26]. Other causes like sports injuries and violent assaults in developed countries. While assault-related injuries were more prevalent Brucoli *et al.* found that in regions with significant alcohol abuse and social dissatisfaction, Assault related injuries are the primary cause of ZMC fracture [27]. It contrasts with our findings where road traffic accidents were predominant. There are various causes of ZMC fracture across different regions of the world. This highlights the influence of social, cultural, and geographic factors. In contrast, our findings emphasize the need for better road safety education and measures in Abbottabad. This is to mitigate the high incidence of road traffic accidents. Treatment option varies globally. It includes different approaches ranging from non-fixation to direct reduction and fixation. Our study supports the use of bone plating. This aligns with the findings of Patrick and colleagues [28]. Studies show that better outcomes with mini bone plate fixation compared to wire osteosynthesis. This highlights the importance of adopting optimal treatment strategies to improve patient outcomes [10]. The changing nature of maxillofacial injuries is highlighted by comparisons with studies from various regions. Changed causes going from road traffic accidents to social attacks feature the impact of social, cultural, and geographic variables on the occurrence of zygomaticomaxillary complex fractures [29]. This explains the need for locally educating people on how to prevent such injuries. The treatment modalities of zygomaticomaxillary complex fracture remain a subject of discussion around the world [30]. Using a variety of hardware options, recommendations range from non-fixation to direct reduction and fixation. While different methodologies exist, ideal circumstances favor decrease and fixation with bone plating, as confirmed by studies supporting mini bone plate fixation over wire osteosynthesis. A better understanding of regional influences on fracture demographics and causes is necessary to understand the changing patterns of maxillofacial injuries. This study shows the significance of customized mediations to relieve common causative factors and highlights the meaning of ideal fracture management modalities.

CONCLUSIONS

The study concluded that the higher occurrence of zygomatic complex fractures in this geographic locality, mainly credited to road traffic accidents. Extraordinarily, the age section of 18-40 years is the most impacted section, confirming this stage as an active phase of life and commitment to adventurous pursuits. These findings emphasize the significance of targeted interventions and preventative measures to reduce the frequency of such injuries, particularly during this active phase of life.

Authors Contribution

Conceptualization: SM, PI
Methodology: TAK, GG
Formal analysis: SM
Writing-review and editing: MR, MAW, PI

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparison of Pain Determination Between Celecoxib Tramadol in Third Molar Surgery

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ABSTRACT

Selecting a reliable and well-tolerated analgesic to manage pain after surgical extraction of the third molar is still a difficult task. **Objective:** To compare the effect of celecoxib and tramadol in managing post-operative pain following third molar surgery. **Methods:** This cross-sectional research was conducted at the Department of Oral and Maxillofacial Surgery, Liaquat University of Medical and Health Sciences, Jamshoro. A total of 100 patients were included and equally allocated into two groups. Group-A received celecoxib, and Group-B received tramadol. Patients were assessed on follow-up visits on the 1st, 3rd, and 5th days post-surgery. **Results:** Data revealed a mean age of 28.72 ± 3.844 years for Group-A (celecoxib), consisting of 30 (60%) males and 20 (40%) females out of 50 respondents. Group-B (Tramadol) exhibited a mean age of 28.28 ±3.511 years, including 29 (58%) males and 21 (42%) females. Preoperational and 1st day post-operational pain scores were similar for celecoxib and tramadol (median 8), with no significant difference (p-value= 0.180 and p-value= 0.874). By the 3rd day, celecoxib patients reported significantly lower pain (median 3, IQR 2-4) compared to tramadol (median 5, IQR 4-6), p<0.001. On the 5th day, celecoxib also had significantly lower pain (median 0, IQR 0-1) than tramadol (median 1, IQR 0-2), p<0.001. **Conclusions:** The study concludes that celecoxib is more effective than tramadol in mitigating pain following third molar surgery.

INTRODUCTION

The surgical procedure of extracting third molar teeth (wisdom teeth) in dentistry includes pericoronitis, disruption to neighboring teeth, related pathology, and non-restorable carious lesions and/or pulpal pathology [1, 2]. Local anesthesia is commonly used for third molar surgery, but more complicated cases may require General Anesthesia (GA) [3]. Inadequately treated postoperative pain can significantly impact the quality of life of patients [4, 5]. Despite the introduction of modern pain control guidelines and pharmacological advancements, the management of postoperative pain in this context is often insufficient [6, 7]. Celecoxib and tramadol (NSAIDs) which are commonly used for pain management and are well known for the inhibition of cyclooxygenase COX1 and COX2 enzymes where COX1 is presented throughout the body and synthesizes protective prostaglandins in tissues such as the gastric mucosa, kidneys, and platelets, while COX2 is primarily expressed during inflammation [8-10]. However, the use of NSAIDs is contraindicated in individuals with peptic ulcers, bleeding disorders, aspirin allergy, or those

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taking anticoagulants or corticosteroids [11]. In such cases, tramadol may be a suitable alternative. Tramadol is a centrally acting mild mu-opioid receptor agonist and inhibits the reuptake of nor-adrenaline and serotonin, making it effective for managing mild to severe pain globally. On the other hand, celecoxib primarily inhibits COX2 [12]. Certain studies have investigated the efficacy of medications like tramadol and celecoxib during third molar surgery, there is limited research comparing the effectiveness of oral celecoxib and tramadol for postoperative pain management after surgical extraction of third mandibular molars.

Hence, the aim of this research is to compare the analgesic potency of these medications. In maxillofacial surgery, third molar extraction is routine but can result in significant postoperative issues [13]. This study evaluated how celecoxib and tramadol mitigate these complications. This study aimed to examine the effectiveness of celecoxib and tramadol in managing postoperative pain following surgery for third molar impaction, thereby contributing to the development of personalized pain management strategies in this surgical domain.

METHODS

The study employed a comparative cross sectional design utilizing a cross-sectional comparative approach and was utilized with a convenient non-probability sampling technique at Oral and Maxillofacial Surgery Department, Institute of Dentistry, Liaquat University of Medical Health and Sciences Jamshoro from Dec 2020 to May 2021. Sample size was calculated through online sample size calculator Openepi Version 3.01 [DEFF*Np (1-p)]/ [(d2/Z21-α/2*(N-1) + p*(1-p)]. Confidence limits as % of 100(absolute +/- %)(d): 5%. A total 100 patients were enrolled and were equally divided in 2 groups of celecoxib and tramadol as Group A and B respectively. The study's ethical approval was provided by research ethics committee of Liaquat University of Medical and Health Sciences, Jamshoro (NO. LUMHS/REC/-980). Patients with either gender from the age 18-45 having mesioangular impacted lower third molar were included. Patients with Gastroesophageal Reflux Disease (GERD), Gastrointestinal Tract (GIT) upset or medically compromised patients having any malignancy, pregnant / lactating women, or patient having NASIDs allergy were not included in this study. Eligible participants who have provided informed consent. Patients were randomly assigned to treatment groups using the Port Chit process. Data was collected by predesigned questionnaire from the patients like postoperative pain score using Visual Analog Scale(VAS) along with age and gender. The VAS ranging from 0 (no pain) to 10 (worst pain imaginable) associated with mesioangular impacted mandibular third molars [5]. The extraction procedure was adhered to standard protocols under local anesthesia administered using traditional nerve block techniques, involving two 1.8 mL cartridges of 2 percent xylocaine with epinephrine 1: 100,000 (sourced from Korea) and supervised by a qualified individual. Surgical procedure involves using a sterile carbon steel surgical blade#15 (Feather Protection Razor Co. Ltd., Japan) for incision and a straight elevator for tooth elevation. Tooth extraction is performed meticulously, aided by circular bur in a slow-speed turbine with copious 0.9% saline irrigation (Searle Ltd., Pakistan), and instruments from Johnson & Johnson (USA). Hemostasis is ensured with sterile gauze (2 x 2) for 30 minutes. Post-surgery, patients receive Tab Augmentin 625mg BD, Tab Sanofi Aventis Palestine Metronidazole, and either Tab Flagyl 400mg BD, Tab Celbexx Celecoxib 100mg, or Tab Tramadol 100mg BD for pain management till next follow-up, alongside 5-day course of GlaxoSmithKline antibiotics (Amoxicillin + clavulanic acid). Follow-up appointments to determine the pain level were scheduled on the 1st, 3rd, and 5th days. The data was analyzed using SPSS version 22.0. Frequencies and percentages were calculated for categorical variables, while mean and SD± will be computed for continuous variables like age and pain score. Normality of pain Score was assessed using Shapiro wilk test. Pain score was skewed (p=0.013). So non-parametric test i.e. Mann-Whitney U test was run to compare pain between two interventions. Other tests were employed as needed, including pre- and post-stratification. Significance was set at $p < 0.05$.

RESULTS

100 eligible participants, evenly split by gender, aged 18 to 45, were enrolled to compare celecoxib with tramadol for pain in third molar surgery. They were divided equally into two groups: Group A (Celecoxib) and Group B (Tramadol). table 1 showed the mean age of the patients with the gender frequency of both the groups.

Table 1: Demographics of Respondents (n=100)

Variables	Celecoxib (Mean ± SD) / N (%)	Tramadol (Mean ± SD) / N (%)
Mean Age (Years)	28.72 ± 3.844	28.28 ± 3.511
Gender		
Male	30 (60%)	29 (58%)
Female	20 (40%)	21 (42%)

Table 2 showed the pain intensity levels for Group A (Celecoxib) during preoperative assessment exhibited mean values of 8.16 and a median of 8. Postoperatively, mean values decreased progressively to 7.92, 3.24, and 0.2 on the 1st, 3rd, and 5th days respectively, with corresponding median values of 8, 3, and 0. In Group B (Tramadol), preoperative pain intensity mean values were 8.34 with a median of 8, decreasing to 7.94, 4.56, and 0.8 on the 1st, 3rd, and 5th days respectively, with corresponding median values of 8, 5, and 1.

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Table 2: Mean and Median of Pain in Two Interventions (n=100)

Pain	Celecoxib		Tramadol	
	Mean	Median	Mean	Median
Preoperational Assessment	8.16	8	8.34	8
Post-Operational Assessment of at 1st Day	7.92	8	7.94	8
Post-Operational Assessment at 3rd Day	3.24	3	4.56	5
Post-Operational Assessment at 5th Day	0.2	0	0.86	1

Preoperational and 1st day post-operational pain scores were similar between celecoxib and tramadol (median 8 for both), with no significant difference (p-value=0.180 and p-value=0.874, respectively). By the 3rd day post-operation, celecoxib patients reported significantly lower pain (median 3, IQR 2-4) compared to tramadol patients (median 5, IQR 4-6), with a p-value of <0.001. On the 5th day, celecoxib also showed significantly lower pain (median 0, IQR 0-1) than tramadol (median 1, IQR 0-2), with a p-value of <0.001 (Table 3).

Table 3: Comparison of Pain at Various Time Points Between Two Interventions (n=100)

Pain Assessment	Celecoxib Median (IQR)	Tramadol Median (IQR)	P-Value*
Preoperational assessment	8 (7-9)	8 (6-9)	0.180
Post-operational assessment at 1st Day	8 (7-9)	8 (7-9)	0.874
Post-operational assessment at 3rd Day	3 (2-4)	5 (4-6)	<0.001
Post-operational assessment at 5th Day	0 (0-1)	1 (0-2)	<0.001

* Mann Whitney Test

DISCUSSION

The challenge of achieving painless surgery persists, particularly in selecting appropriate analgesics. This study aimed to compare the pain determination of tramadol and celecoxib in mitigating pain following third molar surgery, with a focus on identifying the more effective agent in this context [8]. Third molar extraction stands as a common dentoalveolar procedure in maxillofacial surgery, often accompanied by transient postoperative discomfort. Celecoxib and tramadol are both widely employed for managing postoperative pain, trismus, and swelling. However, this investigation delves into the specific roles of tramadol and celecoxib in this surgical context [9]. Zamiri B *et al.*, in 2009 conducted a comparative study involving ibuprofen, tramadol, and celecoxib for pain control post third molar extraction [14]. Their findings revealed superior pain severity reduction with ibuprofen compared to celecoxib at 4 and 8 hours' post-extraction, with both categories exhibiting lower severity relative to the tramadol group. In 2013, Yamaguchi and Sano explored pre-emptive analgesia for lower third molar surgery. They suggested that administering analgesics before surgery could prevent central sensitization resulting from tissue injury, NSAIDs, or acetaminophen, potentially reducing postsurgical peripheral sensitization [10]. However, their findings indicated that the advantage of pre-emptive analgesia using NSAIDs or opioids during lower third molar surgery was not significant in relieving pain [15-19]. Akinbade AO *et al.*, evaluated mean Visual Analog Scale (VAS) scores post-extraction, noting the lowest score in the celecoxib group (32.35 ± 23.96) at 4 hours, followed by ibuprofen (38.96 ± 22.30), and the highest score in the tramadol group (53.31 ± 23.30) at the same interval [15, 20]. Statistically significant differences were observed in mean VAS scores at 4 hours' post-extraction (p-value= 0.003), favoring celecoxib. Celecoxib consistently yielded lower mean VAS scores at 8, 24, and 48 hours' post-extraction, suggesting its superior analgesic efficacy post-mandibular third molar extraction compared to ibuprofen and tramadol. In our study, we assessed pain intensity using the visual analog scale, revealing mean scores of 8,3,0 in patients treated with celecoxib versus 8,5,1 in tramadol-treated patients on the 1st, 3rd and 5th days post-surgery, respectively, with statistical significance at $p < 0.05$. These results suggest that celecoxib demonstrates greater effectiveness in reducing pain compared to tramadol in third molar surgery.

CONCLUSIONS

The study directly compares celecoxib and tramadol efficacy in third molar surgery, with celecoxib showing superior analgesic effects. Preoperative pain reduction on days 1, 3, and 5 was significantly greater with celecoxib compared to tramadol. Although tramadol displayed notable pain relief post mandibular third molar extraction, it was less effective than celecoxib in reducing both pain and trismus.

Authors Contribution

Conceptualization: SKP, SS, SKP
Methodology: EI
Formal analysis: SH
Writing, review and editing: MQ, FH, ZAM

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

Comparative Evaluation of Neck Length, Relative Neck Length and Total Body Height in Cervical Spondylosis Affected and Non-Affected Individual

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ABSTRACT

Anthropometric measurements, including neck length, relative neck length and total body height, have been proposed as potential indicators of cervical spine health, yet their association with cervical spondylosis remains relatively understudied. **Objective:** To compare neck length, relative neck length, and total body height between individuals affected by cervical spondylosis and a non-affected control group. **Methods:** This case-control study was conducted at Department of Anatomy Multan Medical and Dental College (MMDC), Multan from April 2023 to September 2023. Cases were diagnosed with cervical spondylosis and controls were selected from the same population without a history of cervical spine pathology or symptoms. The collected data were analyzed using IBM SPSS, version 27.0. **Results:** Gender distribution revealed females in both cases (63, 60.6%) and controls (59, 56.7%). The age of participants ranged from 25 to 75 years. The mean age for cases was 49.2 ± 12.93 years and for controls was 49.7 ± 13.19 years. The mean neck length among cases and controls was 105.2 ± 17.22 mm and 107.7 ± 20.02 mm, respectively. Regarding relative neck length, cases and controls exhibited measurements of 6.41 ± 1.07 mm and 6.42 ± 1.27 mm, respectively. Height-wise, cases measured 164.4 ± 10.27 cm, while controls measured 168.3 ± 8.53 cm. **Conclusions:** In conclusion, while no significant differences were observed in neck length or relative neck length between cervical spondylosis patients and controls, a notable disparity in height was noted.

INTRODUCTION

Cervical spondylosis, often referred to as neck arthritis or cervical osteoarthritis, is a common degenerative condition affecting the cervical spine, particularly as individual's age. This condition affects the bones, discs and joints in the neck and may cause the following symptoms: neck pain and stiffness, with radiation of the symptoms to the arms and shoulders [1, 2]. The most common cause of cervical spondylosis is advancing age, but heredity and other factors including some lifestyle aspects and prior neck injuries may also lead to the formation of this disease [3, 4]. Disc desiccation and possible future bone spurring due to loss of water content in cultural discs of the cervical spine As people grow older, the discs in the cervical spine progressively lose their water content and elasticity and thereby their ability to withstand pressure and shock. They can lead to the reduction in the size of the spinal canal and the neural foramina therefore causing spinal nerves to be compressed and stimulated [4]. Headache and stiffness of the neck is common and sometimes it becomes severe if one has to bend forward or has to sit or stand for long hours.

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n severe cases where spinal cord compression is established, people may develop weakness in arms and/or legs, coordination issues, or bladder and bowel changes; they should seek medical help [5]. Conservative treatment interventions may include: inactivity or modification of an individual's activities; physiotherapy; various analgesics and anti-inflammatory agents; epidural steroid injections and/or muscle relaxants. [6]. The study varies from the common approach where one, researches only on conventional diagnostic indicators or management procedures; but instead, the study was centered on anthropometric measures including neck length, relative neck length, and total body height as the possible indicators or correlation of cervical spine health [7]. Structural measures are one of the most fascinating approaches that may offer great potential in the dissection of skeletal features and the onset of cervical spondylosis. The human neck, the section when combined with the cervical vertebrae, is of critical consideration as it forms part of the head support as well as affords a host of movements. Thus, changes in the neck dimension or its relative length compared to the rest of the body may impose substantial effects on spinal mechanics and loading[8, 9].

Thus, this study contributes to the existing literature on cervical spondylosis by considering anthropometric markers, namely, neck length, relative neck length, and total body height as potential markers of the cervical spine health, which has been less researched. In the context of Pakistan, where research on cervical spondylosis is limited, this study fills a crucial research gap by exploring a unique aspect of the condition that has not been extensively investigated in the local context. By addressing this gap, the study aims to contribute valuable insights into the structural predispositions or risk factors associated with cervical spine degeneration specifically within the Pakistani population. This study aimed to conduct a comparative evaluation of neck length, relative neck length, and total body height in cervical spondylosis affected and non-affected individuals.

METHODS

This prospective case-control study was carried out in the Department of Anatomy, Multan Medical and Dental College, Multan, from April 2023 to September 2023. The study followed the ethical principles specified in the Declaration of Helsinki and received permission from the institutional review board (Ref: MMDC/IRB/121/24). All participants provided informed consent. The sample size calculation was done using the WHO sample size calculator with an expected frequency of cervical spondylosis set at 13.76% taking a significance level of 0.05 and a margin of error of 5% were utilized [10]. Convenience sampling was used in the study. Cases were diagnosed with cervical spondylosis if CT or MRI reveals osteophytes ≥ 2 mm, moderate to severe disc degeneration (≥ Grade 2, Pfirrmann scale), and facet joint changes (≥ Grade 2, Weishaupt scale). Clinical symptoms, including neck pain (VAS ≥ 4), reduced range of motion (< 60 degrees) and neurological deficits (radiculopathy or myelopathy) and were indicative of cervical spondylosis. Controls were selected from the same population without a history of cervical spine pathology or symptoms. Exclusion criteria included prior cervical spine surgery or trauma, other neurological conditions, systemic illnesses affecting measurements, cognitive impairments and pregnancy/lactation. Anthropometric measurements, including neck length, relative neck length, and total body height, were measured using standardized procedures. The patients were instructed to maintain an upright posture with their neck in a neutral position and to lower their shoulders. The neck length was determined by determining the vertical distance in the outer occipital protuberance as well as the tip of the seventh cervical vertebra using Synapse software. The senior radiologist conducted a cross-check. In order to get the relative neck length, we divided the neck length by the total body height and then multiplied by 100. This method is commonly used to standardize neck length measurements relative to the individual's height [18].

Relative Neck Length (%) = (Total Body Height ÷ Neck Length)×100

The participants stood barefoot against the height rod of the stadiometer to measure their total body height. The outcome of the study was a comparison of anthropometric measurements between individuals with cervical spondylosis and a non-affected control group. Additionally, gender-based differences within the cervical spondylosis group were assessed. Data were analysed using IBM SPSS 27.0. Categorical variables are frequency and percentage. Mean and SD describe continuous variables. Analytical methods included independent sample t-tests to compare cervical spondylosis patients' neck length, relative neck length, and height to controls. Statistical significance was set at $p < 0.05$.

RESULTS

The study comprised 104 cases with cervical spondylosis and an equal number (n=104) of controls. Gender distribution revealed a slightly higher representation of females in both cases 63 (60.6%) and controls 59 (56.7%). The age of participants ranged from 25 to 75 years. Regarding age distribution, participants were categorized into four groups: less than 30 years, 30-44 years, 45-59 years, and 60 years and above. The majority of both cases and controls fell within the 45-59 age group, constituting 45.2% (n=47%) and 44.2% (n=46) respectively, followed by

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30-44 age group (24% vs 23.1%). The mean age for cases was 49.2 ± 12.93 years and for controls was 49.7 ± 13.19 years as shown in table 1.

Table 1: Age and Gender Distribution of Study Participants (n=208)

Variables	Cases N (%)	Controls N (%)
Gender		
Male	63 (60.6%)	59 (56.7%)
Female	41 (39.4%)	45 (43.3%)
Age Groups (Years)		
< 30	9 (8.7%)	12 (11.5%)
30-44	25 (24.0%)	24 (23.1%)
45-59	47 (45.2%)	46 (44.2%)
≥ 60	23 (22.1%)	22 (21.2%)
Age (Years)	49.7 ± 13.19	

Among the cases, the most prevalent symptoms were neck pain 82 (78.8%), followed by radicular pain 54 (51.9%), painful neck movements 52 (50.0%), clumsiness of hands 27 (26%), headache 23 (22.1%) and vertigo 8 (7.7%). Common signs included Spurling's sign (60.6%), stiffness (48.1%), and Lhermitte's sign (47.1%). Radiographic findings indicated straightening 72 (69.2%) and osteophytes 71 (68.3%) as the predominant observations as shown in table 2.

Table 2: Distribution of Cases According to Clinical and Radiographic Findings (n=104)

Cases	N (%)
Neck Pain	82 (78.8%)
Radicular Pain	54 (51.9%)
Painful Neck Movements	52 (50.0%)
Clumsiness of Hands	27 (26.0%)
Headache	23 (22.1%)
Vertigo	8 (7.7%)
Sensory Loss	27 (26.0%)
Motor Weakness	42 (40.4%)
Stiffness	50 (48.1%)
Lhermitte's Sign	49 (47.1%)
Spurling's Sign	63 (60.6%)
Straightening	72 (69.2%)
Osteophytes	71 (68.3%)
Disc Herniation	8 (7.7%)
Narrowing of Disc Space	20 (19.2%)

The mean neck length among cases and controls was 105.2 ± 17.22 mm and 107.7 ± 20.02 mm, respectively. Regarding relative neck length, cases and controls exhibited measurements of 6.41 ± 1.07 mm and 6.42 ± 1.27 mm, respectively. Height-wise, cases measured 164.4 ± 10.27 cm, while controls measured 168.3 ± 8.53 cm. Comparison between cases and controls revealed no significant difference in neck length (p = 0.338) or relative neck length (p = 0.986). However, a statistically significant difference was observed in height between cases and controls (p = 0.003) as shown in table 3.

Table 3: Measurements of Case and Control Subjects' Height, Neck Circumference and Relative Neck Circumference (n=208)

Measurements of Case and Control	Cases (Mean ± SD)	Controls (Mean ± SD)	p-Value[a]
Neck Length (mm)	105.2 ± 17.22	107.7 ± 20.02	0.338
Relative Neck Length (mm)	6.41 ± 1.07	6.42 ± 1.27	0.986
Height (cm)	164.4 ± 10.27	168.3 ± 8.53	0.003

[a] Independent sample t-test

Within the cases group, Male (n=41) and Female (n=63), a gender-based comparison showed significant differences in neck length (p = 0.005) and height (p < 0.001) between males and females. Males exhibited longer necks (111.02 ± 16.85) compared to females (101.40 ± 16.50), whereas females had a shorter stature (160.54 ± 8.83) in contrast to males (170.36 ± 9.52) as shown in table 4.

Table 4: Male and Female Cases Were Compared in Terms of Neck Length, Relative Neck Length and Height (n=104)

Measurements	Male (Mean ± SD)	Female (Mean ± SD)	p-Value[a]
Neck Length (mm)	111.02 ± 16.85	101.40 ± 16.50	0.005
Relative Neck Length (mm)	6.53 ± 1.03	6.33 ± 1.09	0.360
Height (cm)	170.36 ± 9.52	160.54 ± 8.83	< 0.001

[a] Independent sample t-test

DISCUSSION

Cervical spondylosis, a common degenerative disorder of the cervical spine, often presents with neck pain and stiffness, along with neurological symptoms such as numbness and tingling. The hallmark radiographic features of cervical spondylosis include reduced intervertebral disc space and the formation of osteophytes along the vertebral bodies. In advanced stages, cervical spondylosis can lead to spondylotic myelopathy, characterized by impaired upper limb function due to spinal cord compression [11]. Height significantly influences personality traits such as leadership and academic success, with average stature reflecting a complex interplay of factors like nutrition, genetics, ethnicity, and hormones, falling within the 3rd to 97th percentiles, while short and tall statures represent natural variations across diverse populations [12]. In our study, the age of cervical spondylosis patients ranged from 25 to 75 years, with majority falling within the 45-59 age group (45.2%), followed by 30-44 age group (24%), ≥ 60 years' age group (22.1%) and < 30 years' age group (8.7%). This observation was comparable with the findings of Lv Y *et al.*, in 2018 who reported 46.6% patients in 45-59 age group, 24.7 % in ≥ 60 years' age group, 21.7% in 30-44 age group and 7% in < 30 years' age group [13]. The previous study of Alshami AM *et al.*, in 2015 reported that most of patients with cervical spondylosis fell in 30-49 years' age group (35.3%) followed by 50-59 years' age group (32.1%), indicating lower proportion compared to our study [14]. The mean age for cases was 49.2 ± 12.93 years and for controls was 49.7 ± 13.19 years in our study. Singh S *et al.*, in

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2014 also reported a mean age for cases similar to ours which was 49.76 years, but lower mean age for controls which was 39.38 years [15]. Our study revealed a slightly higher proportion of females in both cases (60.6%) and controls (56.7%) compared to males (39.4% vs 43.3%). Alshami AM *et al.*, in 2015 also reported higher proportion of females (73%) compared to males (27%) in cervical spondylosis patients, which are lower than our findings [14]. Another study conducted by Genji L *et al.*, in 2020 showed that the incidence of cervical spondylosis was more in females (22%) than males (16%) [16]. In this study, neck pain was seen in 78.8% patients, radicular pain in 51.9%, painful neck movements in 50.0%, clumsiness of hands in 26%, headache in 22.1% and vertigo in 7.7% patients. A study conducted by RoseBist PK *et al.*, in 2018 reported slightly higher proportion of neck pain (84%), radicular pain (56%), painful neck movements (53%), clumsiness of hands (30%) and headache (25%), but slightly lower proportion of vertigo (9%) in cervical spondylosis patients [17]. Common signs included Spurling's sign (60.6%), stiffness (48.1%) and Lhermitte's sign (47.1%) in our study RoseBist PK *et al.*, in 2018)7also reported similar findings having spurling's sign in 60%, stiffness in 52% and Lhermitte's sign in 47% patients [17]. In our study, cases showed decreased neck length (105.2 ± 17.22 mm) as compared to controls (107.7 ± 20.02 mm) but similar relative neck length in cases (6.41 ± 1.07) as compared to controls (6.42 ± 1.27), although difference was not significant. These findings were consistent with the study of Ahmad SB *et al.*, in 2020, who also reported shorter neck length in cases (104.15 ± 18.9 vs 106.98 ± 19.0 mm) but almost similar relative neck length in cases and controls (6.90 ± 0.89 vs 6.93 ± 0.87) [18]. In present study, the mean height was 164.4 ± 10.27 cm in cases and 168.3 ± 8.53 cm in controls. A study in Lucknow conducted by Singh S *et al.*, 2014 revealed that the average height of individuals with cervical spondylosis was 156.58 ± 8.84 cm, whereas the control group's mean height was 159.54 ± 8.17 cm [15]. This was supported by a study carried out by Ulbrich EJ *et al.*, in 2014 indicating a positive correlation between body height and cervical spinal canal dimensions [19]. Our study also indicated a significant decrease in neck length in females (101.40 ± 16.50 mm) as compared to the males (111.02 ± 16.85). Ahmad SB *et al.*, in 2020 also reported that the mean height in females (159.14 ± 8.88) was lower than males (168.81 ± 8.42) [18]. In another study, these findings were comparable with the study of Taha M *et al.*, in 2022 who also reported slight decrease in neck length in females (109.25 ± 13.97 mm) as compared to males (110.31 ± 12.71 mm). Females had a shorter stature (160.54 ± 8.83) in contrast to males (170.36 ± 9.52) in our study [20]. The limitations of our study included single-center study, small sample size and measurement errors. In future research endeavors, the study should be conducted across several tertiary care medical facilities to establish correlations between various patient variables, thus discerning the risk factors and prevalence of the disease within our population.

CONCLUSIONS

In conclusion, while no significant differences were observed in neck length or relative neck length between cervical spondylosis patients and controls, a notable disparity in height was noted. Furthermore, gender-based variations in neck length and height within the cervical spondylosis group suggest potential anatomical considerations in the pathogenesis of the condition.

Authors Contribution

Conceptualization: MKA
Methodology: MKA, FM, KM, HA, FI
Formal analysis: FM
Writing, review and editing: HA, FI

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Relationship Between the Consumption of Beverage Use and Its Effects on Oral Health

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ABSTRACT

The current study of beverages as likely contributors to the prevalence of oral diseases in the general population has initiated interest in investigating the association of beverage use and its impact on oral health. **Objective:** To explore the relationship between beverage consumption and its impact on oral health. **Method:** Data were gathered from 377 college students for a cross-sectional study by using a convenience sampling technique. The study included male and female students, aged 19-25, excluding those who declined or couldn't communicate in Urdu/English. verbal consent was taken and confidentiality was maintained. A 95% confidence interval and a p-value of equal and < 0.05 were used to identify significant findings. **Results:** The study included 377 medical and dental college students of which 273 (72.4%) were females and 104 (27.6%) were males. Soft drinks were correlated with dental caries (65.1%) which was followed by sensitivity (14.2%), calculus/plaque (10.7%), and tooth staining (10.1%). Tea consumption was associated with dental caries (54.5%). The relationship between beverage type and its impact on oral health was highly significant (p-value < 0.001). Furthermore, the frequency of beverage consumption and its effect on oral health showed significant results, with a p-value of 0.006. **Conclusions:** The findings suggest a significant correlation between beverage consumption and various oral health issues, including dental caries, sensitivity, calculus, and staining.

INTRODUCTION

Youth has been considered a fundamental period of life in terms of food related behaviors. During this period, youth spend more time with their friends and also make different food preferences. Avoiding healthy food and consuming harmful sugar containing drinks can impair the health of the individual badly. Therefore, consumption of soft drinks has been reportedly consumed by youth in larger quantities [1]. Youngsters are specifically inclined to choose carbohydrate-rich soft drinks thus increasing their risk of getting dental cavities more frequently [2, 3]. Sugar-sweetened beverages, which are defined as drinks with added sugars, naturally occurring sucrose or other calorie-sweetening agents, high-fructose corn syrup or concentrated fruit juice, are a common source of dietary sugars. There has been a substantial rise in utilization and ease of use of beverages in many countries during the past 20 years, particularly fruit drinks, sports drinks and carbonated drinks with additional sugar. They are related to several metabolic diseases which are diabetes and cardiovascular disease, and they significantly increase obesity [4]. Some of the beverages have an unsafe impact on the dental as well as on the general health of human beings which include young people and teens [3]. The excessive content of sugar and acids in beverages with cariogenic and acidogenic potential can cause dental caries, enamel erosion, calculus and periodontal problems [5-7]. In addition to containing an excessive quantity of sugar, these drinks are acidic by nature, which immediately lowers the pH of the mouth. Although the saliva's ability to act as a buffer can initially counterbalance this effect,

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continued consumption of sugary drinks can affect the oral health of an individual [8]. Manufacturers and government companies have made efforts to minimize the harmful effects of sugar-containing drinks on dentition and general health. They have adopted various strategies to help reduce the use of beverages which include banning the sale of drinks at schools, restricting advertisements of soft drinks, modifying the composition, and increasing taxation on soft drinks [5]. Dental caries is the most common non-communicable infection throughout the world. Approximately, 2.4 billion people are affected by caries of permanent teeth and 486 million teens are affected with caries worldwide. Treatment of dental caries is expensive, generating costs equal to 5–10% of healthcare budgets in industrialized countries [4]. Therefore, understanding the impact of beverage consumption on oral health is essential for policymakers and healthcare providers to develop strategies that reduce dental caries and other diseases, thereby alleviating the burden on the healthcare system. This study was conducted to investigate the relationship between consumption of beverage use and its effects on oral health.

METHODS

A cross-sectional study was conducted over 2 months from 1st September to 30th October 2023, after obtaining ethical approval from the research and Ethical Review Board Lahore Medical and Dental College (FD/1237/23). The survey was conducted by circulating a close-ended questionnaire among the students of LMDC, Lahore by employing a convenience sampling technique. The Open Epi calculator version 3.01 estimated the sample size to be 330 participants, using a 95% confidence level, 5% precision and a 33% prevalence rate for dental caries [4]. However, the sample size was raised to 377 students to account for possible non-responses and dropouts. This decision was made under the assumption that not all individuals initially recruited will participate. The questionnaire comprised various questions which were asked by conducting face to face interviews with the students of LMDC by the researcher. The participants were asked various questions which were age, gender, types of beverages used, frequency of taking beverages and knowledge of dental effects with consumption of beverages. Different questions were asked about the effects on the oral cavity like generalized sensitivity, generalized staining, calculus/plaque, and dental caries. Students were briefed on the study's aim and procedure. The consent form detailed the study's objectives, procedures, confidentiality assurances and commitment to scientific research. Participants were asked to seek clarity or ask questions about any aspect of the consent form. They were informed of their rights to decline or withdraw from participation at any stage and a pilot survey involving ten respondents was conducted to validate the questionnaire before the start of the study. Students were recruited from Lahore Medical and Dental College, Lahore, consisting of students from any academic year in medical and dental disciplines of both genders, aged between 19 to 25 years. Exclusion criteria included refusal to participate, age outside the 19-25 range, and inability to communicate in Urdu or English. SPSS version 26.0 was used for data analysis and descriptive statistics were calculated for percentages and frequency. Chi-square test of significance was applied to assess any significant differences in beverage intake intensity and oral health outcomes. P-value of 0.05 or less was considered statistically significant.

RESULTS

There were 377 students out of which 104 (27.6%) were males while 273 (72.4%) were female students as shown in table 1.

Table 1: Gender Wise Distribution of the Students of LMDC (n=377)

Type of Students (Gender)	N (%)	Total
Male	104 (27.6%)	377
Female	273 (72.4%)	

Table 2 showed the student knowledge that soft drinks were linked to dental caries 110 (65.1%), followed by generalized sensitivity 24 (14.2%), plaque 18 (10.7%), and tooth staining 17 (10.1%). Tea correlated with caries 60 (54.5%), while alcohol linked to plaque 20 (40.8%) and fruit juices to sensitivity 19 (38.8%). The association between beverage types and oral health effects was significant (P-value < 0.001).

Table 2: Distribution of Student's Knowledge (LMDC) According to the Types of Beverages and Effects on Oral Health (n=377)

Types of Beverages	Effects on Oral Health N (%)				P-Value
	Generalized Staining of Teeth	Generalized Sensitivity	Dental Caries	Calculus/ Plaque	
Soft drink	17 (10.1%)	24 (14.2%)	110 (65.1%)	18 (10.7%)	0.000
Tea	16 (14.5%)	15 (13.6%)	60 (54.5%)	19 (17.3%)	
Alcohol	12 (24.5%)	15 (30.6%)	2 (4.1%)	20 (40.8%)	
Fruit Juices Energy Drinks	13 (26.5%)	19 (38.8%)	15 (30.6%)	2 (4.1%)	

Table 3 showed that participants consuming beverages once daily showed lower chances of tooth staining 13 (18.3%), caries 31 (43.7%), sensitivity 15 (21.1%), and calculus/plaque 12 (16.9%). Those drinking beverages 2-3 times daily were more associated with caries 103 (60.9%). The correlation between beverage frequency and oral health effects was significant (p-Value = 0.006).

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Table 3: Distribution of Student's Knowledge (LMDC) According to Frequency of Beverages Intake and Effects on Oral Health (n=377)

Frequency of Taking Beverages	Effects on Oral Health N (%)				P-Value
	Generalized Staining of Teeth	Generalized Sensitivity	Dental Caries	Calculus/ Plaque	
Once Per Day	13 (18.3%)	15 (21.1%)	31 (43.7%)	12 (16.9%)	0.006
Two To Three Times Per Day	13 (7.7%)	30 (17.8%)	103 (60.9%)	23 (13.6%)	
One To Two Times Per Week	18 (22.0%)	15 (18.3%)	34 (41.5%)	15 (18.3%)	
Rarely	14 (25.5%)	13 (23.6%)	19 (34.5%)	9 (16.4%)	

DISCUSSION

Our study found a significant relationship between higher consumption of soft drinks and dental caries (65.1%), followed by tea (54.5%) and fruit juices (30.6%). Another study was conducted in Saudia Arabia revealed that fizzy soft drinks have a negative impact on teeth (67.83%) and can lead to dental plaque or white patches (61.89% vs. 41.47%) [9]. While other study showed that 50.6% of the students were consuming sugary drinks and had dental caries of 25.7% and 16.5% of calculus [10]. In fact, preliminary evidence suggests that increased consumption of ultra-processed foods and drinks was linked to a higher risk of developing dental caries [11]. An investigation carried out in Saudi Arabia in 2016 showed a direct correlation between the use of beverages and dental caries [12]. A similar study on the impact of beverage use on oral health found that sweetened sugary drinks were associated with dental caries (OR = 1.57), which led to tooth loss in permanent dentition impacts 60% to 90% of children and the majority of adults and teens as shown by WHO report though another study shown by Leena Verma's study revealed that approximately 65% of the students believed that sweets, soft drinks, and chips cause tooth decay ($p < 0.001$) [13-15]. SSD intake was notably linked with increased caries occurrence as indicated by the DMFS indices, leading to a greater likelihood of dental decay [16]. Khairnar MR et al., identified a significant correlation ($p < 0.001$) between dental caries and the frequency of sugary food consumption, alongside tea intake (p-value= 0.02) [17]. A study revealed that alcohol addiction not only impacts overall health but also affects oral health significantly. Alcoholics face elevated risks of developing dental caries and gingival diseases [18]. According to our study, taking beverages once in a day reduces the risks of tooth staining, caries, sensitivity and plaque while frequent intake (2-3 times daily) significantly increases caries risk, showing a strong correlation (p = value 0.006) [19]. Hadilou M *et al.*, in her study, showed that the most common consumption pattern was 1-2 servings (approximately 300 ml per serving) per day among 25% of participants and about 82.73% were aware of dental erosion, and 81.82% knew that carbonated or acidic beverages cause erosion, leading to sensitivity [20]. According to the study results, DMFT showed no association with natural fruit juice or SSB consumption. However, a 4-year prospective study by Tahmassebi JF et al., involving Finnish adults over 30 reported that high SSB consumption increased DMFT by 31% to 33% [4]. On the contrary, Hadilou's M revealed that consuming tea and coffee weekly led to a 13% lower DMFT compared to daily consumption (p=0.01) and so lowers the chances of dental caries [20].

CONCLUSIONS

Beverages are associated with increased caries, calculus, and sensitivity. Consumption of beverages should be reduced, especially in children and youth by continued efforts through policymakers, practitioners' dental public health leaders by oral health education, and clinicians to minimize consumption of beverages for reducing the burden of oral disease.

Authors Contribution

Conceptualization: SHAH
Methodology: SHAH
Formal analysis: ZN, SHAH, SLSS, NGS
Writing, review and editing: SHAH, SLSS, NGS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Parental History of Psychopathology and Attention Deficit Hyperactivity Disorder among Children

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ABSTRACT

Parental history of psychopathology has been linked to an increased risk of Attention Deficit Hyperactivity Disorder (ADHD) in children. Research suggests that genetic and environmental factors contribute to this association, highlighting the importance of early identification and intervention. **Objective:** To determine the association between family history of psychopathology and ADHD among children. **Methods:** This cross-sectional comparative analysis was carried out from December 2019 to June 2020 upon 64 children, presenting with ADHD and their parents, who presented to the General Psychiatric OPD and Child Psychiatric OPD of Department of Psychiatry, Liaquat University Hospital; Hyderabad and Jamshoro and Sir Cowasjee Jehangir Institute of Psychiatry, Hyderabad. Data were recorded onto a structured questionnaire containing inquiries pertaining to basic biodata, sociodemographic details and confirmatory diagnosis. **Results:** The mean age of the sample (children) stood at 9 ± 2 years while the maternal and paternal mean age stood at 33 ± 5 years and 32 ± 3 years, respectively. A majority (83%) of the sample (children) comprised of boys, while the remaining 17% were girls. The most common symptoms of ADHD reported by parents (among children) included aggression, hyperactivity and academic problems. Positive psychiatric history among mother, father and siblings was noted in 39.1%, 32.8% and 48.4% of the cases respectively. **Conclusions:** Parental psychopathology (most notably anxiety spectrum disorders and major depressive disorder) has been found to be associated with ADHD among children.

INTRODUCTION

ADHD is a brain condition where people might struggle with paying attention, being overly active and acting without thinking things through [1]. The prevalence of ADHD among children ranges from 2.2% to 17.8% worldwide and the prevalence is markedly higher (34%) in Pakistan [2]. The etiology of this condition is multi-factorial, and it is known that genetic factors predispose to its development. However, the onset of ADHD, manifestation of clinical symptoms and disease severity is largely dependent on many risk factors. Broadly categorized as either biological or environmental; the risk factors play a major decisive role [3]. Family plays a big role in how ADHD (Attention Deficit Hyperactivity Disorder) works. Some people think it's because of things like genes that run in families, while others say it's because of how the family environment is. It's hard to tell which one has a bigger impact because they're closely connected, but both are thought to be really important [4]. Researchers have hypothesized that the connection between parental psychopathology and ADHD among children also may be due to a shared genetic origin [5]. Literature offers ample evidence, indicative of the fact that both maternal and paternal psychiatric diagnoses are independently associated with offspring ADHD. Reports suggest a significant association between child ADHD and

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parental psychopathology, with the odds being 5.61 times higher than in comparison groups (CI 1.10–28.62) [6]. Whether it's because of genes or the environment, both are thought to affect ADHD through epigenetics. Genes can have an impact through stuff like X chromosomes passed down from the mom or the mitochondrial genome. On the other hand, the environment is always there and can affect ADHD all the time [7, 8]. Reciprocally, ADHD is a significant contributor to parental psychological distress and consequent psychopathology. Studies indicate that children with ADHD can affect family dynamics and parent-child relationships, leading to decreased parental confidence, increased stress and higher rates of parental mental health issues. Children with ADHD often exhibit non-compliant behavior, sibling and peer conflicts, and issues in school settings, further exacerbating parental challenges. This suggests that parents with mental health issues might be more involved in managing their child's ADHD symptoms [9]. The complex relationship between parental psychopathology and ADHD remains indefinable, suggesting a possible 'cycle of cause and effect' that is self-perpetuating, needs further investigation.

This research aimed to determine the association between family history of psychopathology and ADHD among children.

METHODS

This cross-sectional comparative analysis was carried out from December 2019 to June 2020 upon 64 children presenting with ADHD and their parents, to the General Psychiatric OPD and Child Psychiatric OPD of Department of Psychiatry Liaquat University Hospital; Hyderabad and Jamshoro and Sir Cowasjee Jehangir Institute of Psychiatry, Hyderabad. Children (aged 6 to 13 years) with ADHD brought by their parents were included in the study after taking written informed consent from the parents. While children with the history of neurological disease, epilepsy or significant head trauma and adopted children with no biological link to the parents and children of non-consenting parents were excluded from the study. 64 normal children without ADHD along with their both parents were taken as normal controls. Children were selected via non-probability consecutive sampling. Openepi sample size calculator was used for sample size calculation by taking prevalence of parental psychopathology i.e. Anxiety among with ADHD children as 4.3% and with margin of error as 5% and confidence level of 95% [10]. The study was approved by Research Ethics Committee of Liaquat University of Medical and Health Sciences (No. LUMHS/REC/-787). The parents of the children were invited to allow themselves and their children to participate in the study and written informed consent was obtained. Once enrolled in the study, the outcomes of the study were evaluated for assessing the presence of ADHD in children using DSM-5 criteria for ADHD, used for diagnosing based on specified symptom criteria and impairment and the Vanderbilt ADHD Diagnostic Parent Rating Scale which consists of 55 items and was scored based on the frequency of symptoms (never, occasionally, often, very often). The psychopathology among parents was measured via the MINI International Neuropsychiatric Interview 7.0.2, a structured interview with multiple modules, indicated the presence or absence of various psychiatric disorders. Self-made, structured questionnaire was developed which contained inquiries about biodata, sociodemographic, ADHD symptoms and history of ADHD and history of psychopathology among parents. Data were analyzed using Microsoft Excel 2016 and SPSS version 21.0. Qualitative data were expressed as number and percentage. Quantitative data were expressed as mean and standard deviation (mean ± SD). The association between parental psychopathology and child ADHD was measured using Chi-Square test. P value ≤ 0.05 was considered as statistically significant.

RESULTS

The mean age of the sample (children) stood at 9 ± 2 years while the maternal and paternal mean age stood at 33 ± 5 years and 32 ± 3 years, respectively. A majority (83%) of the sample (children) comprised of boys, while the remaining 17% were girls. The majority of the sample either weighed normal or were underweight. Only a small proportion weight more than the desired 5th percentile of the average for their respective age group as shown in table 1.

Table 1: Descriptive Statistics of the Sample

Variables	(Mean ± SD)/N (%)
Children's Mean Age (Years)	9 ± 2
Maternal Mean Age (Years)	33 ± 5
Paternal Mean Age (Years)	32 ± 3
Mean Weight of Children (Kg)	29.3 ± 2.1
Gender Distribution	
Boy	53 (83%)
Girl	11 (17%)
Weight Distribution	
Underweight	23 (35.9%)
Normal	29 (45.3%)
Overweight	12 (18.8%)

The most common symptoms of ADHD reported by parents (among children) included inattention, hyperactivity, impulsivity, aggression, and academic problems as shown in figure 1.

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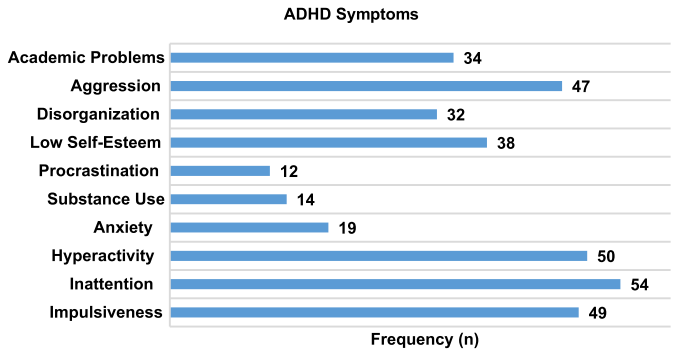

Figure 1: ADHD Symptoms Among Children

Table 2 presented the psychiatric history among parents and its association with ADHD in children. A significant association was found between maternal psychiatric history and ADHD in children, with 23.4% of mothers of ADHD children having a psychiatric history compared to 6.3% in the control group ($p < 0.05$). Similarly, 26.6% of fathers of ADHD children had a psychiatric history, compared to 9.4% in the control group ($p < 0.05$). These findings suggest a notable link between parental psychopathology and the prevalence of ADHD in their children.

Table 2: Psychiatric History Among Parents

Parental History Of Psychopathology		ADHD in Children N (%)		p-Value
		Yes	No	
Mother	Yes	15 (23.4%)	4 (6.3%)	<0.05
	No	49 (76.6%)	60 (93.8%)	
Father	Yes	17 (26.6%)	6 (9.4%)	<0.05
	No	47 (73.4%)	58 (90.6%)	

Table 3 summarized psychiatric diagnoses among parents. Major Depressive Disorder affected 7 mothers (46.7%) and 5 fathers (29.4%). Generalized Anxiety Disorder was found in 3 mothers (20%) and 4 fathers (23.5%). Suicidality was absent in mothers but present in 1 father (5.9%). Panic Disorder occurred in 1 mother (6.7%) and father (5.9%). Specific Phobia was reported in 1 father (5.9%). Obsessive Compulsive Disorder affected 2 mothers (13.3%) and 3 fathers (17.6%). Post-Traumatic Stress Disorder was identified in 1 father (5.9%). Other diagnoses were present in 2 mothers (13.3%) and 1 father (5.9%). Overall, 15 maternal diagnoses and 17 paternal diagnoses were recorded.

Table 3: Psychiatric Diagnoses in Parents of ADHD Children

Diagnosis	Mother N (%)	Father N (%)
Major Depressive Disorder	7 (46.7%)	5 (29.4%)
Generalized Anxiety Disorder	3 (20%)	4 (23.5%)
Suicidality	0	1 (5.9%)
Mania	0	0
Panic Disorder	1 (6.7%)	1 (5.9%)
Agoraphobia	0	0
Specific Phobia	0	1 (5.9%)
Obsessive Compulsive Disorder	2 (13.3%)	3 (17.6%)
Post-Traumatic Stress Disorder	0	1 (5.9%)
Others	2 (13.3%)	1 (5.9%)
Total	15 (100%)	17 (100%)

DISCUSSION

Attention Deficit Hyperactivity Disorder (ADHD) is prevalent among an estimated 17.8% children worldwide with south-east Asian countries, Pakistan in particular, reporting one of the highest (34%) prevalence in the world [11]. The condition is often diagnosed early in childhood and the low mean age of our research participants i.e., 9 ± 2 years, mirrors this fact [12]. The most common symptoms of ADHD reported by parents (among children) included aggression, hyperactivity and academic problems and research from around the world offer diverse finding. International researches indicate similar prevalence rates for these symptoms [13, 14]. Additionally, anxiety and low self-esteem are frequently observed in children with ADHD globally, with approximately 39.1% experiencing anxiety [14]. Comorbid conditions such as learning disabilities and depression are also prevalent, with 36.5% having learning disabilities and 18.9% experiencing depression [14]. The condition (ADHD) is multi-factorial and has a diverse etiology however, Perry GM and Faraone SV has reported a possible link between parental psychopathology and ADHD among children [15]. The link may be due to a shared genetic origin, as reported by Comings DE *et al.*, or be a product of the shared environment and exposure to common predisposing factors [16]. Genetic factors play a role through the mitochondrial genome, inherited from the mother or x-chromosomal factors while environmental factors could influence in either manner, before birth or after the child is born [17, 18]. Nonetheless, the link does seem to exist and this research too lends its weight to this claim with parental psychopathology being a common finding in the study subjects (children with ADHD). Positive psychiatric history among mother, father and siblings was noted in 39.1%, 32.8% and 48.4% of the cases respectively in this research. A study published in the Child and Adolescent Psychiatry and Mental Health journal found that parental psychopathology significantly affects the prevalence of ADHD in children. This research demonstrated similar conclusion as of ours that parental mental health issues, combined with family adversity, substantially contribute to ADHD symptoms in children [19]. Our study further elaborated that the total effect of parental psychopathology on child ADHD symptoms was significant ($p < 0.051$), which explains the importance of addressing parental mental health in managing ADHD in children. A research in the Italian Journal of Pediatrics showed a high correlation between ADHD in children and a positive history of ADHD symptoms in their parents during childhood. This study revealed that 49.1% of fathers and 30.0% of mothers of children with ADHD had features

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consistent with ADHD themselves, compared to only 1.7% in parents of non-ADHD children. The study showed a strong genetic component in the transmission of ADHD, supporting the notion that a family history of ADHD is a critical factor in the disorder's prevalence [20]. The findings from our study show significant psychiatric diagnoses among parents of children with ADHD, with Major Depressive Disorder (MDD) affecting 46.7% of mothers and 29.4% of fathers and Generalized Anxiety Disorder (GAD) present in 20% of mothers and 23.5% of fathers. These results align with another study by Dadashi M *et al.*, which consistently highlights a higher prevalence of psychiatric disorders among parents of children with ADHD [21]. Shen IH *et al.*, suggests that stress to mothers during pregnancy may affect the children adversely and result in psychological impairments. Reciprocally, child ADHD is also a major contributor to parental psychological distress and consequent psychopathology [22]. The findings in our study are consistent with international research, emphasizing the significant association between parental psychiatric history and ADHD in children. The results regarding the prevalence of GAD, OCD and other psychiatric disorders among parents are also supported by international data. A systematic review and meta-analysis revealed that parental depression, particularly maternal depression, is significantly associated with ADHD in children. This relationship is consistent across various studies, underscoring the genetic and environmental influences on ADHD development [23]. Moreover, international research corroborates the presence of other psychiatric conditions among parents of ADHD children. For example, a Canadian study highlighted that parents of children with ADHD often have higher rates of depressive and anxiety disorders, along with other psychiatric conditions such as Obsessive-Compulsive Disorder (OCD) and Panic Disorder [24].

CONCLUSIONS

Parental psychopathology is found to be associated with ADHD among children. The most common psychopathologies were anxiety spectrum disorders and major depressive disorder. In most cases, the psychopathology had been identified prior to the diagnosis of ADHD among children, as per parents' report.

Authors Contribution

Conceptualization: AHR
Methodology: SA, MAA
Formal analysis: AHR, ZAM, AN, AI
Writing, review and editing: ZAM, SA, AN, AI, MAA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

Role of Serum Albumin as Predictor of Postoperative Morbidity and Mortality in Gastrointestinal Surgeries

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ABSTRACT

Serum albumin, a key protein in human plasma, maintains oncotic pressure and transports various substances. In gastrointestinal surgeries, the impact of low preoperative serum albumin on postoperative morbidity and mortality is significant but not fully understood. **Objective:** To determine the role of serum albumin levels as a predictor of postoperative morbidity and mortality in patients undergoing gastrointestinal surgeries. **Methods:** This prospective cohort study was conducted at Department of Surgery – Jinnah Post Graduate Medical Centre, Karachi from January 01, 2021, to December 31, 2021. The study included 86 patients with age range 18 to 45 years and of either gender who had undergone elective gastrointestinal surgeries and had preoperative serum albumin levels measured within 7 days before the surgery. Patients having exploratory laparotomy involving organs other than GIT, those who lost to follow-up and patients with conditions that significantly affect serum albumin levels, such as chronic liver disease or nephrotic syndrome, were excluded from the study. **Results:** Hypoalbuminemia (<3.5 mg/dL) was observed in 61 patients (70.9%), while 25 patients (29.1%) had normal albumin levels (>3.5 mg/dL). All 30-day mortalities occurred in the hypoalbuminemia group ($p < 0.05$). Superficial surgical site infections were significantly higher in the hypoalbuminemia group as well (73.4% vs. 26.6%, $p < 0.05$). Other complications were more frequent in patients with hypoalbuminemia but were not statistically significant ($p > 0.05$). **Conclusions:** The study findings indicate that preoperative serum albumin levels were a significant predictor of postoperative complications in patients undergoing elective gastrointestinal surgeries.

INTRODUCTION

Gastrointestinal surgeries have been known to be linked with substantial morbidity and extended stay at the hospital, with studies reported up 35% of cases, having the complications [1-3]. Infectious complications account for a major proportion of the cumulative mortality and morbidity associated with colorectal surgery [4, 5]. Albumin is a single polypeptide responsible for hemostatic management of colloidal pressure, transport of nutrients in blood, scavenging of free radical for its autoxidizing properties. Moreover, it also serves as anticoagulant and antithrombotic agent through inhibition of platelet function. Albumin is believed to have favorable effects on vascular permeability during state of septicemia [6]. Low serum albumin (termed hypoalbuminemia) is also regarded as a marker for malnutrition [7]. In the early 1950's, it was first noted that poor post-operative outcomes (following colorectal surgery) were yielded among cases with low serum albumin [8]. Kang B *et al.*, reported a higher incidence of concurrent sepsis among patients with low serum albumin; while others drew similar associations of hypoalbuminemia with a higher rate of encountering malnutrition among hospitalized patients. [9, 10]. Though albumin status is often recognized as a useful predictor for outcome following most surgeries, however, the efficacy

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may vary depending on the type of surgery. One such surgery wherein the efficacy of albumin status to serve as a predictor of outcome may be challenged, is gastrointestinal (GI) surgery; owing to the fact that GI surgery patients are often malnourished resulting from restricted oral intake, blocked intestines (or intestines with fistulas), sub-par absorptive ability, and large losses of volume from the alimentary canal [11, 12]. Much of the previous research does not take this potential for bias into account; the predictive ability of hypoalbuminemia is cast into doubt [13]. It is important to generate evidence in this regard and determine whether preoperative hypoalbuminemia is of any predictive value in gastrointestinal surgery patients.

This study was designed to determine the role of serum albumin levels as a predictor of postoperative morbidity and mortality in patients undergoing gastrointestinal surgeries.

METHODS

A prospective cohort study was conducted at Department of Surgery – Jinnah Post Graduate Medical Centre, Karachi from January 01, 2021, to December 31, 2021, via non probability consecutive sampling. After obtaining IRB approval (No.F.2/81/2020-GENL/49066/JPMC), informed written consent was taken from every patient. A sample size of 86 was determined with a 95% confidence interval and a 5% margin of error, taking the incidence of postoperative bowel obstruction as 5.9% [14]. The study included patients with age range 18 to 45 years and of either gender who had undergone elective gastrointestinal surgeries including but not limited to Gastrectomy, Colectomy and Small bowel resection. Pancreaticoduodenectomy (Whipple procedure) and Hepatectomy and had preoperative serum albumin levels measured within last 7 days before the surgery. Patients having emergency gastrointestinal surgeries, requiring exploratory laparotomies and with major systematic illnesses like chronic liver diseases, chronic kidney diseases, sepsis, or patients with severe malnutrition or on albumin supplementation in last 30-days prior to surgery, were excluded from the study. The primary outcome was 30-day postoperative mortality while secondary outcomes included intra-abdominal or anastomotic bleeding, bowel obstruction, intra-abdominal sepsis, localized or generalized peritonitis, superficial surgical site infection, and wound dehiscence. These outcomes were recorded to assess the impact of preoperative serum albumin levels on postoperative complications in gastrointestinal surgeries. SPSS version 23.0 was used for data analysis. Descriptive statistics included mean and standard deviation for continuous variables (e.g., age, serum albumin levels) and frequencies/percentages for categorical variables (e.g., gender, postoperative surgical complications). Patients were divided into 2 groups based on their serum albumin levels (<3.5 mg/dL and >3.5 mg/dL). Chi-square test was used to compare postoperative mortality and morbidity in albumin groups.

RESULTS

The study included 86 patients with a mean age of 37 years (± 4 years) (Table 1). The mean preoperative serum albumin level was 3.62 gm/dL. Among the participants, 49 (57%) were male, and 37 (43%) were female. Hypoalbuminemia (serum albumin <3.5 mg/dL) was present in 61 patients (70.9%), while 25 patients (29.1%) had serum albumin levels >3.5 mg/dL.

Table 1: Descriptive Statistics

Variables	Mean ± SD/N (%)
Age (Years)	37 ± 04 Years
Preoperative Serum Albumin (mg/dL)	3.62 gm/dL
Gender	
Male	49 (57%)
Female	37 (43)
Hypoalbuminemia	
Present (<3.5 mg/dL)	61 (70.9%)
Absent (>3.5 mg/dL)	25 (29.1%)

In Table 2 the postoperative outcomes among patients with GI surgeries. Poor postoperative outcomes occurred in 26 patients (30.3%). The 30-day postoperative mortality rate was 2.3%, with 2 patients dying within 30 days after surgery. The complications included intra-abdominal or anastomotic bleeding in 3 patients (3.5%), bowel obstruction in 1 patient (1.2%), intra-abdominal sepsis in 1 patient (1.2%), and peritonitis (localized or generalized) in 1 patient (1.2%). Superficial surgical site infection was the most common complication, affecting 15 patients (17.4%), while wound dehiscence occurred in 3 patients (3.5%).

Table 2: Postoperative Outcomes

Outcomes	N (%)
30-day Postoperative Mortality	2 (2.3)
Postoperative Complications	
Intra-abdominal or Anastomotic Bleeding	3 (3.5)
Bowel Obstruction	1 (1.2)
Intra-Abdominal Sepsis	1 (1.2)
Peritonitis (Localized/Generalized)	1 (1.2)
Superficial Surgical Site Infection	15 (17.4)
Wound Dehiscence	3 (3.5)
Total	26 (30.3)

Comparison of postoperative complications by serum albumin levels was detailed in Table 3. Patients with serum albumin <3.5 mg/dL (hypoalbuminemia) had higher rates of complications. Specifically, 30-day postoperative mortality was 100% in the hypoalbuminemia group, with no deaths in the group with serum albumin >3.5 mg/dL ($p < 0.05$). Intra-abdominal or anastomotic bleeding occurred in 66.7% of patients with hypoalbuminemia compared to 33.3% in those with higher albumin levels ($p > 0.05$). Bowel

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obstruction, intra-abdominal sepsis, peritonitis, and wound dehiscence were all 100% in patients with hypoalbuminemia, with no occurrences in patients with serum albumin >3.5 mg/dL ($p > 0.05$ for each). Superficial surgical site infection was more frequent in the hypoalbuminemia group (73.4%) compared to those with higher albumin levels (26.6%), and this difference was statistically significant ($p < 0.05$).

Table 3: Comparison of Postoperative Complications by Serum Albumin Levels

Postoperative Complications	Serum Albumin <3.5 mg/Dl N (%)	Serum Albumin >3.5 mg/Dl N (%)	P-Value
30-day Postoperative Mortality	2 (100%)	0 (0%)	< 0.05*
Intra-abdominal or Anastomotic Bleeding	2 (66.7%)	1 (33.3%)	> 0.05
Bowel Obstruction	1 (100%)	0 (0%)	> 0.05
Intra-Abdominal Sepsis	1 (100%)	0 (0%)	> 0.05
Peritonitis (Localized/Generalized)	1 (100%)	0 (0%)	> 0.05
Superficial Surgical Site Infection	11 (73.4%)	4 (26.6%)	< 0.05*
Wound Dehiscence	3 (100%)	0 (0%)	> 0.05
Total	21	5	-

**Statistically Significant*

DISCUSSION

Published evidence hints at a high prevalence (up to 50%) of malnutrition in hospitalized patients and it is often hypothesized to influence patient outcome, affect length of hospital stay, cost, mortality, and morbidity [15]. It is important to note that, hypoalbuminemia is known to be most significantly associated with poor healing of tissues, decreased synthesis of collagen, and formation of granuloma in surgical wounds, eventually leading to delayed wound healing [16]. Traditionally, levels of serum albumin have been assessed prior to surgery for many of the reasons and deemed a reliable prognostic indicator (preoperatively) for a wide array of surgical interventions including (but not limited to) cardiac, general surgery and trauma [17-19]. Research has showcased that albumin < 3.5 g/dL is among the most reliable preoperative predictors of mortality and 30-day morbidity and mortality [20]. Additionally, low serum albumin levels were an independent predictor of acute renal failure, bleeding, coma, need for assisted ventilation, transfusions, systemic sepsis and more than two dozen other adverse outcomes ($P < 0.001$ for all the complications). Galata C *et al.*, claimed clinical hypoalbuminemia (albumin < 4.25 g/dL) to be independently associated with extended hospital stay, and other poor postoperative outcomes. Furthermore, severe hypoalbuminemia (albumin < 3.25 g/dL) was deemed to be associated with mortality by Roy N [21-23]. Studies suggest that in elective procedures, the decision to delay or cancel surgery due to low albumin levels must be weighed against the potential risks and benefits of corrective measures. While albumin supplementation may be effective in improving outcomes, it is not without risks, such as fluid overload and electrolyte imbalances. Moreover, the relationship between albumin levels and post-operative outcomes was complex, and other factors such as overall health status, nutritional state, and surgical technique also play a significant role [24, 25]. Our research yielded poor postoperative outcomes with only 2 30-days mortalities having occurred during the course of the research. The mean serum albumin level noted among patients encountering a poor outcome (morbidity or mortality) was significantly lower than patients with better outcomes; thereby supporting our hypothesis and strengthening the belief that serum albumin level, may be taken as a reliable indicator of disease prognosis (postoperative mortality and morbidity) [18]. Though acute factors, namely: surgical stress and trauma may affect the level of serum albumin, but stratified results published in literature show that even after accounting for such effect modifiers, the serum albumin levels remain a potent predictor of operative outcome [26]. The mean age of the sample stood at 37 years (SD ± 04) which is much lower than the samples of Liang WQ *et al.*, 61 (18-87 years) but similar to others such as Pradeep Ghimire MS that is recorded as 49.69 [27, 28]. The gender ratio was tilted slightly in favor of males in this research with 57% of the sample being male patients. This is similar to the aforementioned studies. The mean serum albumin value among patients encountering an infection fell in the hypoalbuminemia range and this is a strong indicator. Liang WQ, *et al.*, and Pradeep Ghimi et have reported similar findings [27, 28]. Savluk ÖF *et al.*, researched this phenomenon among patients undergoing elective colon, gastric, oesophageal and pancreaticoduodenal surgery and revealed that hypoalbuminemia (especially below 3.25gm/dl) was associated with adverse outcomes, extended hospital stays, and in-hospital mortality [29]. Out research yields similar findings and showcases a synonymous trend of adverse outcome among patients with low levels of serum albumin. In this research, the most common postoperative complication was found to be Surgical Site Infection i.e., 17.4%, among patients (15/86). Multi-institutional research by Hennessey DB *et al.*, on patients undergoing colorectal surgery revealed a similar pattern [30]. Hennessey also claimed that the probability of developing a surgical site infection was higher among patients with a lower median preoperative serum albumin, i.e., 3.0 g/dl or less ($P < 0.001$). The pre-operative mean serum albumin level among patients with postoperative surgical site infection was significantly lower in comparison to the patients without surgical site infection in this present study as well. This was seconded by the work of Udeh CI *et al.*, as well who claimed a 53% complication rate among patients with a preoperative albumin level <3gm/dl [31].

CONCLUSIONS

The study findings indicate that preoperative serum albumin levels were a significant predictor of postoperative complications in patients undergoing elective gastrointestinal surgeries. Patients with hypoalbuminemia (serum albumin <3.5 mg/dL) exhibited

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higher rates of complications, including a statistically significant increase in 30-day postoperative mortality and superficial surgical site infections. Although other complications such as intra-abdominal or anastomotic bleeding, bowel obstruction, intra-abdominal sepsis, peritonitis, and wound dehiscence were more frequent in patients with lower serum albumin levels, these differences were not statistically significant.

Authors Contribution

Conceptualization: AAAA
Methodology: AAAA, AA, SP
Formal analysis: AAAA
Writing, review and editing: MA, AA, MS, AN, SP

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

Diagnostic Accuracy of Apparent Diffusion Coefficient in Differentiating Malignant from Benign Endometrial Lesions, Taking Histopathology as Gold Standard

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ABSTRACT

Endometrial cancer is the cancer of the inner lining of the uterus. Histopathology is considered a gold standard invasive diagnostic test for it. However, Magnetic Resonance Imaging (MRI) based Diffusion-Weighted Imaging (DWI) and apparent diffusion coefficients (ADC) values are non-invasive tests that can differentiate malignant endometrial lesions from benign conditions. **Objective:** To assess the diagnostic accuracy of MR DWI in differentiating benign from malignant endometrial lesions taking histopathology as a gold standard. **Methods:** This cross sectional study was carried out at Radiology Ward Lahore General Hospital Lahore for six months. A total of 132 women between 25-55 years of age, with abnormal vaginal bleeding were included. In all patients, diffusion-weighted MRI (DE-MRI) of the pelvis was done followed by histopathology. DW-MRI and histopathology findings were compared. Data were analyzed on SPSS 20.0. The Sensitivity, Specificity, Positive Predictive Value (PPV), Negative Predictive Value (NPV) and diagnostic accuracy were measured using 2×2 contingency table. P-value of <0.001 was taken as significant. **Results:** DW-MRI diagnosed endometrial cancer in 75 patients while 57 patients didn't show any malignant lesion. Histopathology confirmed endometrial cancer in 79 cases and benign lesion in 53. Out of 75 positive DW-MRI patients, 72 were True Positive (TP). Out of 57 negative DW-MRI patients, 07 were True negative (TN). Sensitivity, Specificity, PPV, NPV and diagnostic accuracy were 91.14%, 94.34%, 96.0%, 97.72% and 92.42% respectively. **Conclusions:** DWI based apparent diffusion coefficients (ADC) can more accurately diagnose endometrial cancers than benign lesions. Hence it can be useful adjunct for diagnosis of endometrial lesions.

INTRODUCTION

Worldwide, endometrial cancers are the commonest gynecological malignancy of females around the age of 60 years. Around 3.4% newer cancer cases are attributed to it. Other benign lesions are polyps, hyperplasia, fibroid and adenomyosis [1]. As per USA cancer registry statistics 2010-2014, annually the new cases of endometrial cancer were 25.7 per 100,000 deaths were 4.6 per 100,000 women and 2.8% new diagnosis during the entire life of women [2]. The organization of International Gynecology and Obstetrics Federation (FIGO) states the surgical staging of the endometrial lesion. Histological grading and lymphovascular and cervical invasion should always be recorded [3]. Endometrial histopathology is gold standard for diagnosis its lesions however it is difficult to perform in cervical or vaginal stenosis patients [4]. MRI is the noninvasive radiological entity of choice for the uterine lesions. Conventional MRI tells about size and extent of the disease but not about lymphovascular penetration [5, 6]. DWI and ADC shows decrease values for various tumors and increased for benign lesions. The endometrial cancers assessment has been reported using DWI and 1.5T MRI [7, 8]. Another study on 119 patients showed lower ADC values

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for malignant than benign lesions and sensitivity and specificity of ADC for detecting endometrial carcinoma as 100% and 90.2% respectively [9]. Similarly, in another study, the sensitivity and specificity of apparent diffusion coefficient taken 88.9% and 100.0% respectively [10]. DWI is a form of MRI that measures the free diffusion of water molecules in body tissues. Recently DWI has got significant value in treating gynecological lesions [11]. Theoretically malignant endometrial lesions show lower ADC values and this low value is associated with histological parameters and vice versa. However, there were other studies that show low ADC values association with prognosis of the cancer[12].

This study aimed to find out DWI based ADC diagnostic accuracy in differentiating benign from malignant endometrial lesions taking Histopathology as a gold standard.

METHODS

This was a cross sectional study done at Radiology ward, Lahore General Hospital, Lahore from 20th August 2018 to 19th February 2019 after taking institutional review board approval vide letter No. AMC/PGMI/LGH/Article/Research No/176/2018. 132 patients were taken, with 95% confidence level, 41.67% endometrial carcinoma prevalence and 86.67% sensitivity and 91.0% specificity of ADC to differentiate between malignant and benign lesions [7]. All females between 25-55 years of age having abnormal vaginal bleeding for more than 3 months without any obvious cause were taken in the study by non-probability, consecutive sampling technique. All patients consent was taken before enrolment. Abnormal vaginal bleeding was defined as heavy regular cycle that occurred every 21-35 days and lasts longer than 7 days and endometrium thickness > 14 mm on ultrasonography. All patients had overnight fast of 8hrs and inj. azithromycin for gut clearance for better MR image visualization The major exclusions were pregnant or lactating women, history of uterine procedure in last 6 months, history of previous other cancers, chemotherapy or radiation, patients with hypertension or bleeding disorders and patients with pacemakers, metallic plates attached or having claustrophobia. All patients undergone DW MRI pelvis on 1.5Tesla MR unit. The total scan time was 3-4 minutes and Images were made with an 8-channel body array coil with the help of lower configuration in supine position with single breath hold to take all sequences at two b values (0 mm2/s, 1000mm2/s). The sequences were T1-weighted fast spin-echo axial plane (T1W FSE), T2-weighted fast relaxation fast spin-echo sagittal, coronal and axial planes (T2W FR FSE), T2- weighted fast relaxation fast spin-echo short tau inversion recovery (T2W STIR FSE) and DWI in the axial plane as shown in table I. Manufacturer's software was used to generate the ADC maps. The T1, T2 and DWI images for endometrial lesions were analyzed by a single radiologist on the MR system monitor. Malignant lesions showed high signal intensity on DWI images with the b value of 1000 mm2 /s and low signal intensity on ADC maps. In benign lesions high signal intensity on DWI corresponded to high signal intensity on ADC maps. The ADC values of all endometrial lesions were calculated manually by drawing a circular region of interest (ROI) on T2 weighted image to include the maximum solid part of the endometrial lesion. The ROI was then manually copied to its ADC map, which automatically generated ADC values. The mean ADC value of the patient was calculated by drawing three individual ROIs at different sections of each lesion. After MRI biopsy of all the patients was done in the concerned oncology department and specimen slides were evaluated for endometrial histopathology (HP) by a single histopathologist. Final diagnosis was established on the basis of HP report and DW-MRI and HP results were compared. Demographic details like age, parity, BMI, menopausal status and marital status) were noted on a predesigned proforma. Data were analyzed by using SPSS 20.0. Descriptive statistics (mean, standard deviation, frequency, percentage) used to summarize, organize, and present data meaningfully and concisely. Age, BMI and disease duration were plotted as mean and standard deviation. Maritalstatus (married/unmarried/widow/divorced), parity (primiparous/multiparous), menopausal status (pre-menopause/post-menopause) and endometrial lesions on ADC and histopathology were plotted as frequencies and percentages. 2×2 contingency table was made to calculate above parameters taking histopathology as gold standard. Stratification for age, disease duration, BMI, marital status (married/unmarried), parity (primiparous/ multiparous) and menopausal status (pre-menopause/post-menopause) was done followed by above mentioned parameters calculation. The sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV) and ADC diagnostic accuracy were measured. P-value of <0.001 was taken significant.

RESULTS

In table 1 the MRI parameters used for pelvic examinations in the assessment of endometrial lesions.

Table 1: MRI Parameters for pelvis examination for endometrial Lesions

S. No	Sequence	T1W FSE	T2W FR FSE	T2W FSE STIR	DWI
1	Plane	Axial	Axial, Coronal ,Sagittal	Oblique	Axial
2	Field of view	25x25	25x25,28x28 27x27	23x23	35x35
3	Matrix Size	328x212	328x212,368x 212,356x232	232x212	78x120
4	No of slices	39	39,34,30	25	39
5	Slice Thickness	3mm	4,4,4mm	3mm	4mm
6	Band Width	25.31Hz	22,27.32, 37.63Hz	22Hz	--
7	Rep/Echo Time	398min	1800/170,6100/ 170,1890/170	4001/170	9800/62

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8	Excitations	1.50	2.50,1.50,1.50	3.0	--
9	Scan Time	3.32min/s	4,3.45,3.20 min/s	4min/s	0.27min/s
10	b Values	--	--	--	00,1000s/mm^2

The mean patient's age was 42.70 ± 8.41 years. The mean disease duration was 5.54 ± 1.32 months. The mean BMI was 28.11±2.50 kg/m^2. Out of 132 patients, 42 were primiparous and 90 patients were multiparius.73 patients were premenopausal and 69 were post-menopausal as shown in table 2.

Table 2: Demographics of study participants(n=132)

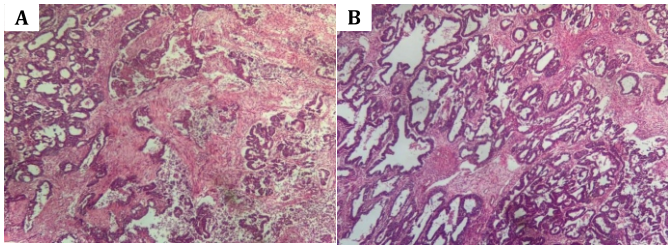
Variables	Category	N (%)	ADC Mean ± SD
Age in years	25-40	48 (36.6)	42.70 ± 8.41
	41-55	84 (63.4)	
Disease Duration in months	< 6	99 (75)	5.54 ± 1.32
	>6	33 (25)	
BMI (Kg/m^2)	≤27	54 (40.91)	28.11 ± 2.50
	>27	78 (59.09)	
Parity	Primiparous	42 (31.82)	-
	Multiparous	90 (68.18)	
Menopausal status	Pre-menopause	73 (55.30)	-
	Post-menopause	69 (44.70)	

In table presented the histopathological findings of both malignant and benign endometrial lesions in a sample of 132 cases.

Table 3: Histopathological findings of malignant and benign endometrial Lesions(n= 132)

S.No.	Endometrial Lesions	N (%)	Endometrial Lesions Catagory	ADC Mean ± SD
1	Serous Carcinoma	11(8.34%)	Malignant 79 (59.85%)	0.676 ± 0.06
2	Endometroid Carcinoma	59(44.69%)		0.518 ± 0.19
3	Adenocarcinoma	6(4.55%)		0.756 ± 0.09
4	Undiferentiated Carcinoma	3(2.27%)		0.891 ± 0.17
5	Endometrial Hyperplasia	21(15.91%)	Benign 53 (40.15%)	1.398 ± 0.24
6	Adenomyoma	4(3.03%)		1.361 ± 0.19
7	Endometrial Polyp	28(21.21%)		1.424 ± 0.30

Histopathological slide of endometrial carcinoma shown in figure 1(a).



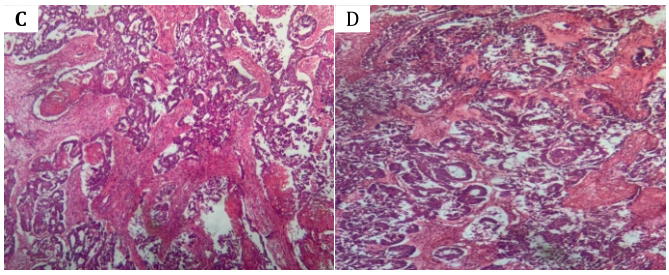


Figure 1(a): Histopathological Images of Low Grade Endometroid Adenocarcinoma (A-D) Confluent Atypical Glands with Very Little Intervening Stroma at High Magnification with H and E Stain

The MRI images in various planes of the patient were shown in figure 1(b).

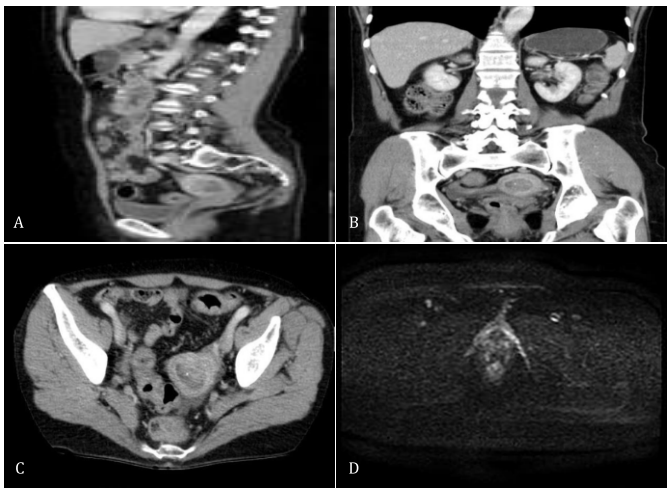


Figure 1 (b): MRI Images of endometrial carcinoma (A) Sagittal section of MRI showing Endometrial Carcinoma (B) Coronal sectional of MRI showing Endometrial Carcinoma (C) Axial section of MRI showing Endometrial Carcinoma (D) DWI Axial section showing endometrial carcinoma.

Regarding the accuracy of ADC, out of 132 cases, DW-MRI supported the diagnosis of endometrial cancer in 75 cases while histopathology (HP) confirmed endometrial cancer in 79 cases. On the other hand, DW-MRI supported the diagnosis of endometrial benign lesions in 57 cases while histopathology (HP) confirmed endometrial benign lesions in 53 cases. Out of 75 positive DW-MRI patients, 72 were true positive (TP) and 03 were false positive (FP). Out of 57 negative DW-MRI patients, 07 were true negative (TN) and 50 were false negative (FN). P value was significant (0.0001). Sensitivity, specificity, PPV, NPV and ADC diagnostic accuracy was 91.14%, 94.34%, 96.0%, 87.72% and 92.42% respectively as shown in table 4.

Table 4: Diagnostic accuracy of ADC taking histopathology as Gold Standard(n=132)

Results	Negative Histopathology	Positive Histopathology	P-Value
Positive DWI Results	72 (TP)*	03 (FP)***	0.0001
Negative DWI Results	07 (FN)**	50 (TN)****	

The diagnostic accuracy of the ADC was demonstrated by its impressive metrics: a sensitivity of 91.14% indicated

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that the test correctly identified 91.14% of true positive cases, reflecting its ability to detect the presence of the condition when it was actually present. With a specificity of 94.34%, the ADC effectively identified 94.34% of true negative cases, showcasing its ability to confirm the absence of the condition. The Positive Predictive Value (PPV) of 96% meant that 96% of individuals who tested positive genuinely had the condition, while the Negative Predictive Value (NPV) of 87.72% confirmed that 87.72% of those who tested negative were truly free of the condition. Overall, the diagnostic accuracy of 94.42% signified that the ADC correctly identified the condition in 94.42% of all cases, reflecting its high reliability and effectiveness in clinical settings (Figure 2).

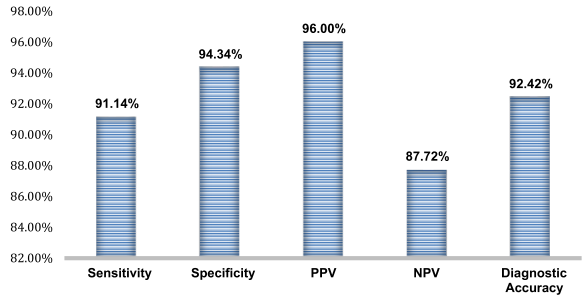

Figure 2: Diagnostic Accuracy of ADC

In table 5 stratification of diagnostic accuracy with respect to age groups, duration of symptoms, BMI, marital status, parity and menopausal status was also done. The post stratification diagnostic accuracy for age group 25-40 and 41-55 years were 97.92% and 89.29% respectively. The post stratification diagnostic accuracy for duration of symptoms in less than 6 and more than 6 months were 90.91% and 96.97% respectively. Similarly post stratification diagnostic accuracy with BMI below 27 and above 27 groups were 98.15% and 88.46% respectively. Post stratification diagnostic accuracy for all married females was 92.42% primparous and multiparous groups had a post stratification diagnostic accuracy of 97.62% and 90%. Similarly, premenopausal and postmenopausal groups post stratification diagnostic accuracy was 97.26% and 86.44% respectively as shown in table 5 all had p value of <0.001.

Table 5: Stratification of Diagnostic Accuracy with Various Parameters

Variables	Category	Positive on both DW-MRI and Histopathology (TP) n	Negative on both DW-MRI and Histopathology (TN) n	Sensitivity %	Specificity %	PPV %	NPV %	Diagnostic Accuracy %
Age (Years)	25-40	15	32	100.0	96.97	93.75	100.0	97.92
	41-55	57	18	89.06	90.0	96.61	72.0	89.29
Duration of Symptoms in Months	< 6	57	33	89.06	94.29	96.61	82.50	90.91
	>6	15	17	100.0	94.44	93.75	100.0	96.97
BMI Kg/m^2	≤27 (N=54)	36	17	100.0	94.44	97.30	100.0	98.15
	>27 (N=78)	36	33	83.72	94.29	94.74	82.50	88.46
Married	N=132	72	50	91.14	94.34	96.0	87.72	92.42
Parity	Primiparous (N=42)	26	15	100.0	93.75	96.30	100.0	97.62
	Multiparous (N=90)	46	35	86.79	94.59	95.83	83.33	90.0
Menopause	Pre menopause (N=73)	32	39	96.97	97.50	96.97	97.50	97.26
	Post menopause (N=59)	40	11	86.96	84.62	95.24	64.71	86.44%

Note: P-value for all of above mentioned parameters is <0.000

DISCUSSION

Our study emphasized the diagnostic accuracy of ADC (92.42%) in differentiating benign from malignant endometrial lesions keeping histopathology as gold standard. This has been supported by a number of studies. Yamada and their colleagues studied that ADC had significantly higher diagnostic performance for predicting histopathology grade and was a more useful indicator predicting survival in patients with endometrial lesions. [13]. Similarly, Deng L *et al.*, studied ADC value enhances confidence in preoperative endometrial cancer evaluation [14]. ADC values in another study was correlated with histologic tumor grade and it was concluded that ADC on MRI is a useful predictor of endometrial malignancy [15]. Quan Q *et al.*, in their study concluded similar findings that ADC values were important to diagnose endometrial lesions, grade risk and prognosis [16]. In another study it was concluded that ADC is a non-invasive technique that has the potential to preoperatively differentiate between low-grade and high-grade endometrial tumors [17]. Mean age in our cohort was 42.70 ± 8.41 years and diagnostic accuracy of ADC of 92.42% while Abdel-Latif M and Mosaad HS in their study have reported a little higher age group i.e. 56.15 years (± 8.229) in their study with a diagnostic accuracy of 84.6% for endometrial carcinomas [18]. Çavuşoğlu M *et al.*, have studied 52 post-menopausal cases with mean age of 57 ± 10 and found the diagnostic accuracy

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of 92.9% for DW1 images in cases of endometrial lesions [5]. Derbyshire AE *et al.*, in their study on 74 women reported that obesity (BMI34-81) is a risk factor for endometrial carcinoma, which increases further with increase in BMI. In our cohort we found 59.09% cases of high BMI [19]. Bae H *et al.*, in their study on 175 patients reported different tumor diameter ($p < 0.001$), signal intensity and heterogeneity on DWI ($p = 0.003$) for disease risk. They concluded that DWI can differentiate different levels of malignant lesions in endometrial lesions [20]. Keriakos NN and Darwish E *et al.*, reported that DWIs with ADC had sensitivity and specificity of 80% each in endometrial lesions and mean ADC value was 0.8×10^{-3} mm^2/s. Our values of sensitivity and specificity (91.14%, 94.34% respectively) show even better results than this. We could not record the mean ADC values in our study [21]. Moharamzad Y *et al.*, reported in their systemic review and meta-analysis on 269 malignant and 208 benign lesions that combined (95% CI) sensitivity and specificity of mean ADC values were 93% and 94% respectively which was comparable to the values i.e. sensitivity: 91.14%, specificity: 94.34% [21]. Gharibvand MM *et al.*, concluded in their study on 22 patients of abnormal vaginal bleeding the mean ADC value was lower for endometrial cancer than those with benign endometrial lesions, the difference was not significant ($P = 0.13$) however ADC values equaled 90.91 and 9.09 for sensitivity and specificity to differentiate benign from malignant lesions, with an equal of 50% for positive and negative predictive values. In our cohort we found the PPV of 96.0% and NPV of 87.72% [22]. Petrila O *et al.*, in their study concluded that out of 92 cases 77 cases ADC values showed similar results as that of histopathology of endometrial carcinoma showing a diagnostic accuracy of 83.69% for endometrial cancers [23].

CONCLUSIONS

It was concluded that ADC has high diagnostic accuracy to differentiate malignant from benign endometrial lesions. Hence in future it can be used as non-invasive adjunct diagnostic tool.

Authors Contribution

Conceptualization: SS[1]
Methodology: SS[2], FS
Formal Analysis: FS, ZN
Writing, review and editing: SS[2], FS, SHD, ZN, FA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Comparative Analysis of Post-Operative Analgesia Duration in Laparoscopic Cholecystectomy: Intraperitoneal Bupivacaine Versus Bupivacaine/ Buprenorphine Combination

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ABSTRACT

Successful pain management following Laparoscopic Cholecystectomy (LC) is essential for a speedy recovery for patients. Intraperitoneal (IP) administration of analgesics, particularly bupivacaine and buprenorphine, offer promising approach to alleviate post-operative pain with minimized systemic side effects. **Objective:** To compare the duration of post-operative analgesia in patients undergoing laparoscopic cholecystectomy who receive either intraperitoneal bupivacaine alone or a combination of bupivacaine and buprenorphine. **Methods:** The quasi experimental study was conducted at Department of Anesthesiology, Farooq Hospital, Islamabad from April 2023 to September 2023. Patients scheduled for elective laparoscopic cholecystectomy for symptomatic cholelithiasis or other gallbladder diseases were included. The sampling methodology used was convenience sampling, with patients divided into two groups through the lottery method. Patients were assigned into two groups (55 patients in each group). Group A intraperitoneally received 25 ml dilution of bupivacaine (0.25%) in normal saline. Bupivacaine (0.25%) and buprenorphine (0.3mg) dissolved in normal ub6p B compared to Group A (9.26 ± 1.28 vs. 3.08 ± 1.04 hours, $p < 0.001$). **Results:** The mean BMI of participants was 29.79 ± 3.44 kg/m^2 Group A had 36 (65.5%) women and group B 41 (74.5%). The mean duration of post-operative analgesia was much greater in Group B (9.26 ± 1.28 hours vs. 3.08 ± 1.04 hours, $p < 0.001$). **Conclusions:** The combination of bupivacaine and buprenorphine offer post-operative analgesia in laparoscopic cholecystectomy with longer duration as compared to bupivacaine alone which is also statistically significant ($p < 0.001$).

INTRODUCTION

Laparoscopic Cholecystectomy (LC) remains as one of the most important milestones in surgical intervention in the field of surgical disease treatment of the twenty-first century. However, managing the post-operative pain for those patients who had this procedure is still a challenge [1]. It is a major shift from the traditional open method of cholecystectomy and provides patient with minimally invasive methods that clearly have several advantages in terms of post-operative pain management, duration of the hospital stay, rate of recovery and the scarring. Ever since the introduction of the method in the late 1980s, this method has become the standard for addressing symptomatic cholelithiasis and other gallbladder disorders [2, 3]. Laparoscopic cholecystectomy distinguished by employing multiple small incisions that are between 5 to 10mm in average, through which a small camera system and special gadgets inserted into the abdominal cavity [4]. These instruments provide the surgeon with fine control and enhanced magnification of the region being operated; thus enabling the surgeon to extinguish the gallbladder

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effectively without harming other tissues in the region [5]. The techniques applied regarding postoperative pain control in LC patients include systemic, regional, and neural blockade and local anesthetic techniques used during the surgery [6]. Among those, intraperitoneal applications local anesthetics has been emerged as potentially valuable addition to traditional approaches to pain relief [7]. Common to this procedure has been the use of bupivacaine – a long acting local anesthetic which has been used in several volumes of IP administration to manage pain at site of surgery in LC. When performing surgical procedures, surgeons introduce bupivacaine into the peritoneal cavity at the end of the surgery with the purposes of post-operative pain relief and minimizing the need for using systemic opioids [8, 9]. Bupivacaine is a local anesthetics drug that offers prolonged postoperative pain relief, it has a certain duration of action and therefore may require supplemental doses for further analgesia. Buprenorphine, an agonist at μ-opioid receptor is another drug that is given consideration as a contender to be added in combination with budivacaine for prolonging the duration of post-operative analgesia with a reduction in the side effects associated with opioids [10, 11].

This study aimed to expand current knowledge by investigating better pain management options among patients undergoing laparoscopic cholecystectomy by comparing duration of analgesic effect in patients those who receive intraperitoneal bupivacaine alone with those who receive a combination of bupivacaine and buprenorphine. Furthermore, it also answers a particular research question related to Pakistan to provide information on specific pain control measures applicable to the country that will improve on perioperative nursing care studies within the region.

METHODS

The current study was quasi experimental study. The work in this single center research took place in the Department of Anesthesiology, Farooq Hospital, Islamabad over a period of six months from April 2023 to September 2023. Approval was obtained from the institutional review board (FH/IRB/75). Any adverse events or protocol deviations were documented and reported promptly to the IRB. Informed consent was obtained from all participants prior to enrollment in the study. A sample size of 110 cases was determined using WHO calculator (www.openepi.com) with 55 patients allocated to each group, based on an 80% power of the test, a 5% level of significance, and an assumed mean duration of post-operative analgesia. In the bupivacaine group, the mean duration was estimated to be 3.07 ± 0.46 hours, while in the bupivacaine plus buprenorphine group, it was anticipated to be 9.60 ± 2.19 hours [11]. The study inclusion consisted of adult patients (aged 18 years and above) scheduled to undergo elective laparoscopic cholecystectomy for symptomatic cholelithiasis or other gallbladder pathologies. Patients with contraindications to laparoscopic surgery, known allergies to study medications, history of chronic pain syndromes, or significant comorbidities compromising surgical outcomes were excluded from the study. The sampling methodology used was convenience sampling, with patients divided into two groups through the lottery method. Patients in Group A intraperitoneal received 25 ml dilution of bupivacaine (0.25%) in normal saline. Patients in Group B received intraperitoneal infiltration of bupivacaine (0.25%) plus buprenorphine (0.3mg) diluted in normal saline. The primary outcome measure was the mean duration of post-operative analgesia, defined as the time from completion of surgery to the first request for rescue analgesia (opioid analgesics). The data were entered into SPSS version 25.0, and the results were analyzed. Descriptive statistics, including mean values with standard deviations (mean ± SD), were used to analyze numerical variables like age and post-operative analgesic duration. An independent sample t-test and Mann-Whitney U test were used to compare post-operative analgesia duration between groups, with a significance level of $p < 0.05$. Gender frequencies and percentages were given using the Chi-square test. Data were stratified by age and gender to adjust for effect modifiers. Post-stratification independent sample t-tests were performed, with a significance level of $p < 0.05$.

RESULTS

This study has shown that in Group A, the mean age was 47.2 ± 8.4 years while Group B had a slightly higher mean age of 48.5 ± 7.6 (p value=0.62). The distribution of gender within the groups was fairly balanced, with Group A consisting of 39 males (45.88%) and 46 females (54.11%), while Group B had 44 males (51.76%) and 41 females (48.23%). Group A had a mean BMI of 27.5 ± 7.6, whereas Group B had a slightly lower mean BMI of 26.3 ± 6.4. In Group A 31 individuals (36.47%) were diagnosed with hypertension , while in Group B had 26 individuals (30.59%) with the condition, as shown in table 1.

Table 1: Demographic Characteristics between Group A and Group B

Variables	Overall N (%)/ (Mean ± SD)	Group A N (%)/ (Mean ± SD)	Group B N (%)/ (Mean ± SD)	p-Value
Gender				
Female	77 (70.0%)	36 (65.5%)	41 (74.5%)	0.298[a]
Male	33 (30.0%)	19 (34.55)	14 (25.55)	
Age Groups (Years)				
25-35	13 (11.8%)	6 (10.9%)	7 (12.7%)	0.756[b]
36-45	43 (39.1%)	22 (40.0%)	21 (38.2%)	0.542[b]
46-55	39 (35.5%)	19 (34.5%)	20 (36.4%)	0.853[b]
56-65	15 (13.6%)	8 (14.5%)	7 (12.7%)	0.771[b]
Age (Years)	45.67 ± 9.61	45.93 ± 9.58	45.42 ± 9.71	0.782[b]
BMI (Kg/m^2)	29.79 ± 3.44	29.27 ± 3.20	30.32 ± 3.62	0.085[c]

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a Chi-square test; b Independent sample t-test; c Mann-Whitney U test.

The mean duration of post-operative analgesia was much greater in Group B (9.26 ± 1.28 hours vs. 3.08 ± 1.04 hours, p < 0.001), as shown in table 2.

Table 2: Between Group Comparison of Mean Duration of Post-Operative Analgesia

Variables	Group A (Mean ± SD)	Group B (Mean ± SD)	p-Value
Duration of Analgesia (Hours)	3.08 ± 1.04	9.26 ± 1.28	< 0.001[a]

a Mann-Whitney U test.

Subgroup analysis based on gender, age, and BMI further supported the significant difference in the duration of post-operative analgesia between the two study groups, as depicted in table 3. Regardless of gender, age group, or BMI, patients in Group B experienced a substantially longer duration of post-operative analgesia compared to those in Group A (p < 0.001)(Table 3).

Table 3: Between Group Comparison of Mean Post-Operative Analgesia Hours with Respect to Gender, Age, and BMI

Variables	Group A N (%)/ (Mean ± SD)	Group B N (%)/ (Mean ± SD)	p-Value
Gender			
Female	2.97 ± 1.01	9.30 ± 1.37	< 0.001
Male	3.27 ± 1.08	9.12 ± 1.00	< 0.001
Age Groups (Years)			
25-35	3.05 ± 0.82	9.22 ± 0.80	0.001
36-45	3.07 ± 1.10	9.31 ± 1.66	< 0.001
46-55	3.13 ± 1.06	9.25 ± 1.11	< 0.001
56-65	2.96 ± 1.12	9.15 ± 0.99	< 0.001
BMI (Kg/m^2)			
< 30	3.07 ± 1.08	9.37 ± 1.43	< 0.001
≥ 30	3.10 ± 0.96	9.05 ± 0.97	< 0.001

a Mann-Whitney U test.

DISCUSSION

The mean duration of post-operative analgesia is a critical aspect in assessing pain management efficacy following laparoscopic cholecystectomy. Intraperitoneal bupivacaine administration has traditionally been utilized to mitigate post-operative pain in this procedure, while combining bupivacaine with buprenorphine shows promise for extending analgesic duration and improving patient outcomes [12, 13]. The efficacy of intraperitoneal bupivacaine alone versus bupivacaine plus buprenorphine is analyzed, considering their respective roles in optimizing post-operative pain control and patient satisfaction. Our study participants exhibited a mean age of 45.67 ± 9.61 years, with a majority being female (70.0%). This is in concordance with the findings of Chaudhary SM *et al.*, who found the mean age to be almost similar at 47 years. 56 ± 9.24 years and female patients are more in number as compared to male patients (70%) [14]. Current results are consistent with the study by Khurana S *et al.*, who reported that the mean age was 48.87 ± 11. Laparoscopic cholecystectomy was done in 90 patients, and the average age was 41 years [11]. Such consistent demographic characteristics across various studies add to the external validity of our results and indicate homogeneity in the patient population receiving this surgical intervention [11, 12]. The results of the present study showed that there was a statistically significant difference in the mean duration of post-operative analgesia between both the groups, and the mean duration was found to be significantly longer in the group that received bupivacaine combined with buprenorphine compared to the group that received intraperitoneal bupivacaine alone (9.26 ± 1.28 vs 3.08 ± 10) findings are in line with the studies of Khurana S *et al.*, in 2016 and Chaudhary SM *et al.*, in 2017, where they also found that the combination of bupivacaine and buprenorphine has significantly increased analgesia duration as compared to bupivacaine only [11, 14]. More specifically, Khurana S *et al.*, observed a mean duration of analgesia of 9.60 ± 2.19 hours in the combination group as compared to control group to be 3.07 ± 0.46 [11]. Similar results were found in study of Chaudhary SM *et al.*, in 2014, where the mean duration of post-operative analgesia was significantly longer with intraperitoneal bupivacaine combined with buprenorphine (9.43 ± 1.08 hrs) compared to intraperitoneal bupivacaine alone (3.05 ± 1.18 hrs; p=0.000) [14]. These consistent findings across studies support the effectiveness of adding buprenorphine to bupivacaine to prolong the postoperative pain relief in patients who underwent laparoscopic cholecystectomy [10, 13]. The patients in the study were considerably younger (34.6 ± 12.5 years) than the general population of patients who undergo surgery and anaesthesia; the mean duration of anaesthesia after surgery was 4.6 ± 3.7 hours with bupivacaine only as mentioned by Sharma CS *et al.*, in 2014 [15]. Similarly, a randomized clinical trial done by Williams *et al.*, conclusively demonstrated greater pain reductions after administrating bupivacaine along with buprenorphine as compared to the plain BPV group (mean difference 1.8 points, 95% confidence interval 0.6 to 3.0, P = 0.003). These findings align with our results, reinforcing the enhanced analgesic efficacy of combining bupivacaine with buprenorphine over bupivacaine alone [16]. his finding aligns with Manan A *et al.*, in 2020, who reported a mean post-operative analgesia duration of 0.99 ± 0.51 hours in the normal saline group and 16.53 ± 2.65 hours in the bupivacaine group (p < 0.001) [17]. Further, the study of Mahajan L *et al.*, in 2020 revealed that there were statistically significant differences in the post-operative analgesia duration between the groups; the bupivacaine combined with buprenorphine group had the longest duration of 11.5 ± 0.9 hours, the bupivacaine only group had 7.5 ± 0.9 hours [18]. Similarly, Arabzadeh A *et al.*, in 2021 found a similar pattern, where the postoperative analgesic

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durations were significantly longer in the bupivacaine with buprenorphine group compared to the bupivacaine-only group, thus supporting the repeatability of this finding in prior studies [19]. Moreover, Deshmukh P *et al.*, in 2021 demonstrated prolonged analgesic duration with the buprenorphine-bupivacaine combination, supporting our findings and providing further evidence for its efficacy in extending post-operative pain relief [20]. A notable limitation of the present study was the lack of comparison in terms of the complications or side effects linked to the combination therapy, which is an essential component of patient care.

CONCLUSIONS

This study demonstrates the efficacy of intra-peritoneal bupivacaine plus buprenorphine in extending the post-operative analgesia duration in patients who have undergone laparoscopic cholecystectomy as highlighted by the large difference in the mean durations between the treatment groups 9.26 ± 1.28 hours versus 3.08 ± 1.04 hours; $p < 0.001$.

Authors Contribution

Conceptualization: HAH

Methodology: HAH, RS[1], KI, AZ, RS[2]

Formal analysis: RS[1], TA

Writing, review and editing: KI, AZ

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Assessment of Effective Learning Transfer at Workplace after a Formal Faculty Development Program

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ABSTRACT

Higher education institutions use Faculty Development Programs (FDPs) as organized learning opportunities to improve the abilities, knowledge and skills of its faculty members. **Objective:** To evaluate the faculty development program using Kirkpatrick Model and acknowledging the program's importance in medical education. **Methods:** A non-probability purposive sample of 27 faculty members was used in the quantitative quasi-experimental design. Pre- and post-tests or intervention were conducted as part of the CBL facilitation skills training included in the faculty development program after three and six months, with a particular emphasis on CBL facilitation skills comprising four domains: teaching skills, teacher knowledge, student happiness, and environmental factors. **Results:** The analysis revealed that participants demonstrated significantly higher mean scores across all four domains in the second evaluation (post-test/ intervention) compared to the first evaluation (pre-test/ intervention). Each domain showed a $p<0.05$, indicating statistically significant improvements. These results suggest that the CBL facilitation skills training program was effective in enhancing participants' skills. Moreover, the evaluation reached level 3 of the Kirkpatrick model, signifying a positive transfer of learning to the workplace, with observed improvements in teaching skills and behavior change among participants. **Conclusions:** Faculty development programs were mandatory for learning transfer and improving teaching skills at workplace. Proper program evaluations were equally important to see whether learning transfer was actually happening at workplace or not.

INTRODUCTION

There has been a notable increase in medical faculty development programs in the past ten years. Many educational organizations and medical schools today provide a range of activities and programs to assist faculty members enhance their abilities as instructors and educators in response to emerging educational trends in teaching and evaluation [1]. These programs are very effective in making the faculty more competent. They tend to learn a lot from these programs and most of the institutions in Pakistan are now having regular workshops to train the faculty. The ideas for educational development are most often generated by the Individuals who take part in faculty development programs and they also carry out educational development projects [2]. Still, there hasn't been much acknowledgement of the efficacy and influence of FDPs on participation in academic activities. As a result, assessing how these FDPs enhance faculty members' capacity for measuring student learning, technology adaptations, research efficacy, and teaching efficacy has become imperative [3]. When faculty members regularly complete FDPs, the institution's overall performance—both in terms of their own teaching and students' learning is

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dramatically enhanced. When an FDP achieves institutional objectives, it is considered fully resourced from an institutional perspective. From an individual perspective, the level of faculty commitment to institutional values and objectives determines how much an institutionally responsive FDP will involve them [4]. During faculty development programs there should be more prominence on individual needs and evaluating them to institutional priorities. If the needs of participants are not compromised they may not have enough motivations to transfer back to the workplace whatever they have learn through the journey [5]. Once these needs are met and all criteria are achieved then the FDP start the uphill journey of the institution. A deeper comprehension of the effects of FDPs on teachers, students, and institutions can be attained through program evaluation. Numerous evaluation methods can be used to assess the impact of these initiatives, but Kirkpatrick's model of program evaluation is the most widely employed [6]. This model's features include its ease of use, assessment of a small number of variables, evaluation criteria that are simple to understand, independence of individual and environmental variables, and the absence of the requirement to gather baseline data and learner performance. Kirkpatrick's model evaluates training programs' efficacy on four levels: (a) trainee response to the training experience (including the training experience); (b) learner learning outcomes and increases in knowledge, skill, and attitude toward the attendance experience (i.e., the extent to which attendees learned the content following training). This level is often assessed by the use of a pretest and posttest; (c) behavior changes and improvements made by the students (i.e., if the knowledge was used in the workplace); and (d) outcomes (the training's final influence) [7]. Program evaluation is carried out at all four levels of Kirkpatrick model with more emphasis on level 3 and 4 to see the effective learning transfer and behavior change of faculty at workplace and its long-term results which can be materialized by a dynamic and energetic FDP. It effectively leads to the faculty's skills enhancement in all the five domains, i.e., curriculum support, organizational mentoring, teaching, assessment and organizational leadership [8]. In medical education, teacher professionalization is crucial because only skilled educators can provide outstanding instruction. Curricula are constantly updated in higher education in particular to take into account the growing body of knowledge, innovative teaching methods, and instructional technologies. Additionally, theoretical models were put forth to enhance instructional strategies [9]. Behavioral change model is one of them; it aims to change the way teachers behave in the classroom. Another is the development model, where teachers shift their attention from themselves to the material and then back to the students (first facilitating passive learning, then encouraging active learning). Subsequently, the Conceptual Change Model was presented, which holds that instructors' beliefs about education mirror their goals and methods. All activities that improve teachers' skills, Knowledge and behaviors are part of faculty development. Teachers improves their skills and learn to put their knowledge into practice to help student develop [10, 11]. Learning is a complex process for teachers and professional. For implementation of appropriate alternatives to improve or change teaching practices the cognitive and emotional engagement is mandatory. Researchers attempt to identify when and how transfer occurs and to offer strategies to improve transfer. The primary aim of education and learning is to enable individuals to gain knowledge and abilities in formal, structured settings such as classrooms or training sessions. Transfer effectively happens when the program occurring environment is same as the setting in which new knowledge and skills will be applied 10. The simulation and related approaches can be used by Effective faculty development to facilitate in-situ learning. Programs should be developed that stimulate learning and reflection among faculty, raising their self-awareness as teachers [12]. The ongoing self-directed development are completely dependent on it rather than the need to primarily have "teacher-directed" interventions. The process of applying previously gained knowledge and skills to new FDPs are designed keeping in mind the theories of learning transfer. It is tried to keep the FDP atmosphere as close to workplace atmosphere as possible, secondly hands on activities like role playing almost mimics the actual situation. It is also kept in mind while planning an FDP, is to keep the content of the FDP as per the caliber of the participants. Hence, teaching skills developed by FDPs play a vital role in learning transfer. Better the training programs better will be learning transfer.

The study's aim is to assess faculty development program using Kirkpatrick Model and acknowledging the program's importance in medical education.

METHODS

The study was carried out at the Islamic International Medical College in Rawalpindi. A non-probability purposive sampling technique was used for data collection. Inclusion criteria was that participants must be current faculty members, completed the formal faculty development program, currently engaged in teaching, and provide informed consent. Exclusion criteria was participants who did not complete the formal faculty development program, and without teaching role. 27 faculty members were enrolled in the quantitative quasi-experimental study design, after ethical clearance from the college's ethical

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review committee. Using the G-power sample calculator, 27 faculty members were selected for this research. The sample size calculation formula in GPower differs based on the particular test were doing. The formula for calculating sample size for a two-sample t-test (independent groups) is: n= (Zα/2+Zβd) 2n = Where: n = sample size per group, Zα/2= Z value corresponding to the significance level (e.g., 1.96 for a two-tailed test with alpha = 0.05). Zβ= Z value corresponding to the desired power (e.g., 0.84 for 80% power) and ddd = effect size (Cohen's d). The study conducted for six months, from January 2023 to June 2023. In January a workshop as a part of FDP was conducted on CBL facilitation skills. Consent forms were signed by all participants and their willingness to participate in research was taken after explaining the research process. After that a pre-test (14 questions) was taken on CBL facilitation skills and at the end of the workshop a post-test (14 questions) was also taken. Participants then went to their workplace and after 03 months of the workshop participants were assessed at their workplace while they were taking CBL session at their workplace (phase 1) CBL facilitation skills evaluation checklist was used, the checklist was derived from center for community health and development at the University of Kansas. Checklist was mentioned as, open for use for all. Some modifications were made in checklist according to the CBL facilitation skills format and it was then sent to a group of senior medical educationists and they validated the checklist and then the checklist was used. Checklist was divided into 4 domains for the evaluation of facilitators at workplace. These domains were teaching skills (7-questions), teachers' knowledge (6-questions), students' satisfaction (5-questions) and environmental factors (3-questions). Same process was again repeated after 06 months of workshop at the workplace. This study was approved by Islamic International Medical College Institutional Review Board (IRB) "Ref No. Riphah/IIMC/IRC/23/3009. Making ensuring the informed consent procedure was understandable and transparent for each and every participant. Data entry and analysis was carried out with SPSS version 25.0. The statistical analysis was carried out in accordance with the ethical guidelines as follows: Over the course of two rounds, descriptive statistics, such as averages and standard deviations, were computed for every domain on the Case-Based Learning (CBL) checklist. For non-normally distributed data, Paired t-tests were used to compare the mean scores of each domain between the two rounds. A significance threshold of 0.05 was chosen.

RESULTS

The demographic graph information about the participating respondents, who can be assumed to be faculty members in most cases, by the academic rank, gender, age, and years of experience. To begin with, it was of crucial importance to note that there were 3 associate professors, 12 senior lecturers and 11 lecturers. All the information gleaned from the graph and other sources was detailed and structured as follows. Associate Professors had 3 female respondents, no male and all of the respondents was over 50 years old and have more than 15 years of experience. Senior Lecturers 12 female respondents, 1 male. All of the respondents were under 45 years old. All of the respondents had more than 10 years of experience. Lecturers had 10 female respondents, 1 male. All of the respondents were under 40 years of age. All of the respondents had more than 5 years of experience. Total participants had 27 people, with 25 females and 2 males, see figure 1.

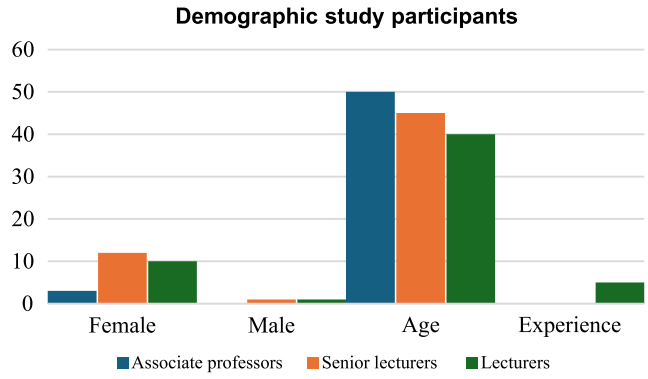

Figure 1: Demographic Study of the Participants

Results show that the intervention has been successful and the participants' knowledge substantially improved after the workshop regarding the subject. The p-value calculated was highly significant and indicated the learning transfer and successful intervention. The difference in mean values and standard deviation calculated for pre and post-intervention were also highly suggestive of successful intervention as shown in table 1.

Table 1: Case-Based Learning (CBL) Facilitation Skills (n=54)

Intervention	Mean ± SD	p-Value(*)
Pre-Intervention	9.92 ± 2.431	<0.001
Post-Intervention	13.28 ± 0.890	

Note (*) Paired sample t-test

Participants in the study were trained on CBL facilitation skills via a workshop as a part of FDP. Later on, at workplace they were evaluated on this skill by a CBL facilitation skill checklist comprising of 4 domains. This evaluation process corresponds to the level 3 (Behavior) of Kirkpatrick model. Each of the participants was evaluated and observed at workplace twice with a gap of three months. Data collected after 3 months of workshop was labelled as group 1 result and after 6 months from workshop collected data were labelled as post-intervention results. Within the individual domains, each and every question's separate mean was calculated and then overall mean of domains were calculated. Means of Pre-intervention and Post-intervention of all 4 domains were compared and p-value was found out by means of paired t-test as shown in table 2.

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Table 2: Improvement Skills by Domain of CBL Checklist

Variables	Pre-Intervention (Mean ± SD)	Post-Intervention (Mean ± SD)	p-Value
Teaching Skills	3.50 ± 1.53	4.85 ± 0.192	<0.001
Teacher's Knowledge/ Transfer of Learning	3.38 ± 1.80	4.57 ± 0.567	0.004
Students' Satisfaction	3.60 ± 1.46	4.91 ± 0.188	<0.001
Environmental Factors	3.47 ± 1.81	4.68 ± 0.176	0.12

There were two groups indicate Pre-intervention and Post-intervention. The mean values of Post-intervention were much higher as compared to mean values of Pre-intervention indicating the improvement in teaching skills, increased transfer of learning, enhanced students' satisfaction and conducive environmental factors for all these to happen at workplace. Results showed that all the domains of CBL checklist have p-values below 0.005 indicating significant increase in all the domains of CBL. The standard deviation values were also calculated and the lesser standard deviation values of Pre-intervention were highly indicative of improvement in all 4 domains. These results clearly show that the intervention has been successful (CBL workshop) in improving the teaching skills of medical teachers at workplace and in return enhancing the learning transfer. Checklist on the basis of which different domains were graded. The checklist was divided into four domains, each with a specific number of items. Each item was rated on a scale (e.g., 1 to 5), where 1 indicates "needs improvement" and 5 indicates "excellent." The evaluation checklist was built on testing four principal domains such as Teaching Skills, Students' Satisfaction, Teachers' Knowledge/Transfer of Knowledge, and Environmental Factors. The items were rated on the following scale: 1= Not done, 2= Poor, 3= Fair, 4= Good, 5= Excellent. Domain-wise scoring was found below; overall scoring was also provided: Teaching Skills: 7-35, Students' Satisfaction: 5-25, Teachers' Knowledge/Transfer of Knowledge: 6-30, Environmental Factors: 3-15. The minimum total score that can be obtained was 21; the maximum one was 105. This scoring system allows one to determine teachers' performance with references to multiple indicators.

Table 3: Checklist of Testing Four Domains

S.No.	Teaching Skills	Rating				
1	Conduct Sessions as Scheduled in the Timetable	1	2	3	4	5
2	Is Punctual in Starting Sessions	1	2	3	4	5
3	Makes his/her Expectations Clear to the Group and Ensure Pre Reading of Resource Provided	1	2	3	4	5
4	Clarifies Students' Expectations of the Group Activities and the Facilitator's Role	1	2	3	4	5
5	Promotes Efficient Use of Time	1	2	3	4	5
6	Is Flexible and Supportive to Group	1	2	3	4	5
7	Use Body Languages to Communicate (i.e., Nods Head, Leans Forward, etc.)	1	2	3	4	5
Students' Satisfaction						
1	Promotes Active Listening (i.e., Listens Attentively; Quotes Students During Discussion)	1	2	3	4	5
2	Helps Each Student to Take a Turn at Leading Discussions	1	2	3	4	5
3	Gives Each Student a Chance to State his/her Opinion about Case and Makes Sure it is Heard by all by Actively Involving the Learners in the Group Process	1	2	3	4	5
4	Clarifies Students' Expectations of the Group Activities and the Facilitator's Role	1	2	3	4	5
5	Insists that Only One Person Speak at a Time	1	2	3	4	5
Teachers' Knowledge / Transfer of Knowledge						
1	Deflects Guesses into a Search for Knowledge and Understanding from Learning Resources	1	2	3	4	5
2	Helps the Group to Assume Responsibility for Collective and Individual Learning	1	2	3	4	5
3	Clears Student's Misunderstandings in Subject and Align the Session with LOS	1	2	3	4	5
4	Keeps the Group "on Track"	1	2	3	4	5
5	Provides Constructive Positive Feedback	1	2	3	4	5
6	Recognizes his/her own Limitations (e.g., "I don't know" will read it and Discuss it Later on)	1	2	3	4	5
Environmental Factors						
1	Creates a Supportive Environment for Open Discussion	1	2	3	4	5
2	Facilitates Resolution of Interpersonal Conflicts	1	2	3	4	5
3	Helps to Establish Clear Ground Rules at the Beginning of Session	1	2	3	4	5

DISCUSSION

Teaching skills were crucial when one was working as an educator. These skills enable teachers to keep their classrooms engaged and interested in learning. Faculty development programs include all activities that improve teachers' knowledge, skills and behavior thus improving teaching skills [12, 13]. In this study the teaching skills of the participants were improved by using the training program. Improvements in teaching skills including the teacher's knowledge were evaluated by CBL facilitation checklist domain results which showed marked increase in each domain mean values indicating the improvement in teaching skills at workplace. These results were taken after the Training program. Efficient and skillful teachers make better nations. It was very important for teachers to improve their teaching skills as well so that they can deliver their best at the workplace. The previous study findings indicate that, framework dominated by informal learning, faculty development may be best seen as all "actions, planned and undertaken by faculty members themselves or by others working with faculty, aimed at enhancing teaching [14, 15].The concept of transferability in learning has different aspects. Effective practice and mindful abstraction can increase learner's transfer. The process of examining one's experiences for similarities was known as Abstraction. Methods used for abstracting knowledge include, what was learned. In this study the learning transfer was observed at the workplace by researcher and recorded through the CBL facilitation checklist results. Participants were observed and evaluated twice at their workplace on CBL evaluation checklist domains to see the

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transfer of learning, results clearly showed that the learning transfer has occurred and the faculty development program has been successful. After careful analysis, we categorized these influencing factors included learner characteristics, programme design characteristics, and educational environment characteristics. The literature that was currently in publication uses a similar classification system, which was congruent with our thematic analysis results [16]. Regardless of the setting or reasons for participation, the faculty development program aim was for participants to leave with and apply new information and perspectives. While producing faculty development episodes that were effective was vital, achieving maximum impact calls for a methodical strategy that includes establishing a supportive practice environment where participants may apply what they have learned [17, 18]. "Finding out what it would need for learning to obtain utility value throughout transitions to different contexts or learning spaces has been essential for as long as learning psychology has existed". We used the concept of past experience (CBL workshop) also referred to as transfer source which affected the learning and performance in a new situation (workplace) also referred to as transfer target [19, 20]. Behavior change at workplace was directly observed by researcher at workplace. CBL facilitation skills checklist was also used to see the behavior change. By behavior change we mean that there was modification of participants' actions, attitudes, and habits to improve their performance productivity and well-being at workplace. This all-in return leads to better workplace environment with increased harmony, employee satisfaction and learning transfer. People were accustomed to seeing emotions and ideas as actions that have the potential to be positive and significant when supporting faculty development in personnel issues. However, when it comes to a scenario involving individuals in an organization, the interactional behavior between the professors and others in their immediate vicinity should be the main focus. Since a faculty member's words or actions have an impact on members of the organization and have implications for the desired outcome. Measuring behavior was meant to determine what has to be adjusted or prepared differently in order to produce a better outcome. In this instance, the training participants were assessed based on several actions to help them become more effective facilitators. In the available literature, the effectiveness of training and transfer intention was usually based on self-reported feedback by faculty, claiming increased teaching effectiveness after faculty training. However, the intervention with the maximum impact on the transfer process was still not well known and remains under-researched [21, 22]. Positive results were seen after the data analysis was completed. Kirkpatrick model level 3 explains the behavior change at workplace corresponds. The workplace faculty development program leads to learning transfer.

CONCLUSIONS

Faculty Development Programs FDP a highly useful tool for raising student satisfaction and faculty performance at work. By doing this, faculty members may quickly assess their own performance levels and the results of their efforts. In order to determine how beneficial these programs were for both faculty and students, as well as what changes must be made to further enhance faculty teaching abilities and learning transfer, thorough assessments of these programs were also necessary.

Authors Contribution

Conceptualization: SA
Methodology: AQ, WPQ, WH
Formal analysis: AQ, WA
Writing, review and editing: MOS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Original Article

Length of Hospital Stay in Patients Related with Moderate Fluid Resuscitation and Aggressive Fluid Resuscitation in Acute Pancreatitis

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ABSTRACT

Due of the intricacy of their illness and the possibility of complications, patients with acute pancreatitis may need to stay in the hospital longer or shorter, approach used. **Objective:** To compare the treatment of moderate fluid resuscitation with aggressive fluid resuscitation in acute pancreatitis patients as well as duration of hospital stay. **Methods:** It was cross-sectional study conducted in the Department of Medicine Muhammad Teaching Hospital Peshawar, with duration of six months, from July 2023 to December 2023. A total number of participants was (N=170) in this study. The age of patients was >16 years included both male and female. There were two groups, first group was moderate fluid resuscitation and second group was aggressive fluid resuscitation each group consists of patients n=85. **Results:** A total number of participants was N=170 and age range was 16-60 years and mean age was 38.5±2.5 years. The frequency of male and female patients was 105.8% and 94.1%. The results indicate that median hospital stay length 4 to 8 days in the aggressive group and 3-5 days in the moderate-resuscitation group. **Conclusions:** In response to treatment, and the emergence of complications were more important to determine patient long stays in the hospital for pancreatitis, even though the decision between aggressive and moderate fluid resuscitation may have a minor effect.

INTRODUCTION

The impulsive inflammation of the pancreas is known as acute pancreatitis. An organ situated beneath the stomach, the pancreas is essential to blood sugar management. Inflammation of the pancreas can result in symptoms such as excruciating stomach pain. Gallstones, one of the most frequent causes, can obstruct the pancreatic duct and cause inflammation. Pancreatitis can develop from long-term excessive alcohol consumption. Pancreatitis can be brought on by abdominal injuries, such as those sustained in falls or auto accidents [1]. The moderate fluid resuscitation strategy is to gradually restore fluid balance while avoiding the dangers of excessive resuscitation. usually entails giving out fluids at a rate of one to two liters every day. Continual fluid administration or smaller boluses (about 250–500 mL every 4-6 hours) may be used, contingent on the patient's state and therapeutic response. The aggressive fluid resuscitation method, which is frequently utilized in cases of shock or severe dehydration, is to quickly restore the volume of blood in circulation. usually entails giving fluids at a rate of more than two liters per day; depending on the severity of the condition, this can sometimes reach 4-6 liters or higher. Large boluses of fluid—typically 500–1000 mL spread over 30–60 minutes—are frequently

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administered; these might be repeated as needed depending on the patient's response and continued losses [2]. Pancreatitis is an adverse effect of some drugs. Pancreatitis can result from blood triglyceride levels that are abnormally high. Pancreatitis can be brought on by bacterial or viral illnesses, such as the mumps or viral hepatitis. One of the main signs of acute pancreatitis is severe abdominal pain. Usually starting abruptly, the pain is felt in the upper abdomen and sometimes spreads to the back. Here is more information about acute pancreatitis and severe abdominal pain: many people describe the discomfort as gnawing and ongoing. It could be continuous or sporadic [3]. Some patients say it feels like they've been stabbed. Though it can also be felt on the left or right side, the pain typically starts in the middle of the belly, right below the sternum, or in the upper abdomen. It could spread between the shoulder blades and extend to the back. Eating or drinking, particularly during large or fatty meals, might make the pain worse. Patients can have increased pain [4]. Intravenous (IV) fluid replacement is a fundamental component of treatment for acute pancreatitis. Fluid loss may result from acute pancreatitis as a result of decreased oral intake and vomiting. IV fluids aid in the replacement of lost fluids and the maintenance of proper hydration, preventing dehydration a critical condition for the proper functioning and recuperation of all organs [5]. Hypotension, or low blood pressure, can result from dehydration and worsen tissue damage and organ perfusion. IV fluids assist in preserving normal blood pressure, which guarantees sufficient blood flow to essential organs [6]. Staying properly hydrated is essential for preserving kidney function, particularly in individuals suffering from acute pancreatitis, since kidney damage can arise as a consequence of the illness. IV fluids aid in maintaining renal perfusion and guard against acute kidney damage [7]. IV fluids are necessary in severe cases of acute pancreatitis, especially those that are compounded by fluid shifts and third-spacing. Hypovolemic shock is a potentially fatal situation in which there is insufficient blood volume to perfuse the tissues. Electrolyte abnormalities, such as hypokalemia or hypocalcaemia, can result from acute pancreatitis because of things like vomiting and fluid loss. Electrolyte-containing IV fluids can assist in reversing these imbalances and preserving appropriate electrolyte levels [8]. If a patient cannot take oral intake, dextrose solutions may be added to their IV fluids to avoid tissue breakdown and to provide them energy. This keeps the body's nutritional needs met while pancreatitis is in its acute stage. I/V fluid administration decisions are made by doctors based on a variety of parameters, including JVP, a useful tool for fluid status assessment. Fluid resuscitation can only be carried out safely and successfully with the help of comprehensive patient assessment, clinical judgment, sophisticated monitoring tools, and adherence to clinical guidelines [9]. Longer hospital stays are sometimes necessary for patients with moderate to severe pancreatitis, particularly if they experience consequences including pancreatic necrosis, contaminated pancreatic fluid collections, or organ failure. Depending on the severity of their ailment and well they respond to treatment, their hospital stay could last anywhere from a few weeks to several months or even longer. The length of hospital stay can be considerably increased in the event of difficulties [10]. The highlights the usefulness of the BISAP score in predicting severe acute pancreatitis and lays the groundwork for its validation across various centers. This work aims to explain how treatment affects creatinine, hematocrit, and urea levels by examining the effects of fluid resuscitation on biochemical markers and systemic inflammation. For example, patients who require surgery to address problems such as infected necrosis can require a longer hospital stay for recuperation and post-operative care. Patients may need nutritional support in certain situations, such as enteral or parenteral nutrition, which could lengthen their hospital stay until they are able to tolerate oral intake sufficiently. The duration of hospital stay is also affected by the underlying causes of pancreatitis. For example, if gallstones are the source of the pancreatitis, patients may need treatments like cholecystectomy (removal of the gallbladder) and have to stay longer in hospital [11]. The duration of hospital stay is mostly determined by how the patient responds to initial care and therapies. While patients with chronic symptoms or consequences may need a longer hospital stay for continued care, those who demonstrate improvement and stability of their condition may be home early [12].

The aim of this study was to compare the treatment of moderate fluid resuscitation with aggressive fluid resuscitation in acute pancreatitis patients as well as duration of hospital stay.

METHODS

A cross-sectional study was conducted in the Department of Medicine Muhammad Teaching Hospital Peshawar. The duration of this study was 6 months, from July 2023 to December 2023. A total number of participants was (N=170) in this study. The age of patients was >16 years included both male and female. There were two groups, first group was moderate fluid resuscitation and second group was aggressive fluid resuscitation each group consists of patients n=85. The median hospital stay length was 5 days in the moderate fluid resuscitation group and 6 days in the aggressive resuscitation group. Inclusion criteria: diagnosed acute pancreatitis, organ failure, necrosis, hemodynamic instability. Exclusion criteria: heart failure, pregnant, breastfeeding, and pancreatic

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cancer. Bedside Index for Severity in Acute Pancreatitis, or BISAP, is a straightforward clinical scoring system for determining the severity of acute pancreatitis. Higher scores denote greater severity. The score goes from 0 to 5. To measure the mental stress, SIRS,>60years, and pulmonary fluid buildup. Pancreatitis Outcome Model for Severity and Intrahospital Mortality is referred to as PAN-PROMISE. This is a more thorough scoring method to estimate the risk of mortality and severity in patients with acute pancreatitis. A combination of clinical and laboratory parameters, such as the following, determine the score: The levels of urea, creatinine, Hematocrit and SIRS. The ratio of participants in Group A to Group B, the expected effect size, and the standard deviation were taken into account. IRB was taken from the Ethical review committee (MTH/EC/76/2022). For comparing means between two independent groups, the sample size for each group can be calculated using the formula: $n=(\Delta/\sigma Z\alpha/2+Z\beta)2$. Where: $Z\alpha/2$ value for the significance level (e.g., 1.96 for a 5% significance level with a two-tailed test). $Z\beta$ value for the desired power (e.g., 0.84 for 80% power). Δ is the effect size, the expected difference in means between the two groups. σ is the pooled standard deviation of the outcome measure. Medical records, standardized questionnaires, and direct measurements were used in the data collection process. For normally distributed data, the means of Groups A and B were compared using the Mann-Whiteny U-test. Data were analyzed statically by SPSS. 26. P value <0.05 showed that the variables were very significant.

RESULTS

A total number of patients N=170 with acute pancreatitis patients were evaluated in order to determine. Overall, N=170 patients were randomly assigned into two groups; first group was moderate fluid resuscitation n=85 and second group were aggressive fluid resuscitation n=85 patients. The demographic patient characteristics were split equally between the two experimental groups. The patient age range was 16-60 years and mean age was 38.5±2.5 years. The age range frequency of patient from 16-30 years was 32.3%. The frequency of age range from 31-45 years was 76.4%. The frequency of age range from 46-60 years was 58.8%. The frequency of male and female patients was 105.8% and 94.1%. After just 1st, 2nd and 3rd day in the hospital, some patients 41.1%, 68.2% and 24.7% were stay hospital with acute pancreatitis treatment. The patients of acute pancreatitis were conduct lab test such as Creatinine (80-83), Hematocrit (76-79) and Urea (70-74). Some patients were SIRs 17.6% which indicate severe illnesses including sepsis, septic shock, or multiple organ failure syndrome can develop from SIRs. A predictive tool for determining the severity of acute pancreatitis and forecasting patient outcomes is the Bedside Index for Severity in Acute Pancreatitis (BISAP) score was 40(43-47). The PAN-PROMISE score was used to estimate the probability of mortality in patients with acute pancreatitis was 15(18-21), see in table 1.

Table 1: Demographic Characteristics of Study Participants (n= 170)

Variables	IQR N (%)
Tumor Grade	
16-30	55 (32.3%)
31-45	65 (76.4%)
46-60	50 (58.8%)
Gender	
Male	90 (105.8%)
Female	80 (94.1%)
Medical Issue	
Acute Pancreatitis Disorder	170 (100%)
Hospital Stays	
1 Day	70 (41.1%)
2 Days	58 (68.2%)
3 Days	42 (24.7%)
Biochemical Variables	
Creatinine mg/dL (IQR)	65 (80-83)
Hematocrit % (IQR)	61 (76-79)
Urea mg/dL (IQR)	68 (70-74)
SIRs	30 (17.6%)
Moderate Fluid Resuscitation	85 (50%)
Aggressive Fluid Resuscitation	85 (50%)
BISAP Score (IQR)	40 (43-47)
PAN-PROMISE Score (IQR)	15 (18-21)

According to our results to found that, there was no significant difference in the development of moderate and severe pancreatitis, which consists of 32 %, 41.1% and 41.1%, 49.9% in moderate and aggressive fluid resuscitation group, odd ratio relative risk [95% CI, 2.10 (0.67-4.15)] and [95% CI, 1.10 (0.33-2.12)]. The necrotizing pancreatitis was observed 3.5% of patients in the moderate-resuscitation group and 16.4% in the regressive fluid group The proportion of patients with renal failure was 2.3% and 22.3%, respectively, an odd ratio [95% CI, 1.43(0.14-3.33)]. The respiratory failure, kidney failure, invasive treatment was shown in table 2.

Table 2: Primary and Secondary Outcomes of Study Participants (n=85)

Variables	Moderate Fluid Resuscitation N (%)	Aggressive Fluid Resuscitation N (%)	Odd Ratio 95% CI N (%)
Moderate Pancreatitis	27 (32%)	35 (41.1%)	2.10 (0.67-4.15)
Sever Pancreatitis	35 (41.1%)	42 (49.4%)	1.10 (0.33-2.12)
Local Complications			
Necrotizing Pancreatitis	3 (3.5%)	14 (16.4%)	1.43 (0.14-3.33)
SIRS			
12 Hours	24 (28.2%)	49 (57.6%)	3.17 (1.2-4.65)
24 Hours	10 (11.7%)	31 (36.4%)	1.20 (1.99-3.11)
48 Hours	6 (7%)	12 (14.1%)	0.66 (0.12-1.95)
72 Hours	2 (2.3%)	21 (24.7%)	2.76 (0.57-2.95)
Other Outcomes			
Invasive Treatment	6 (7%)	22 (25.5%)	2.50 (0.85-4.14)
Nutritional Support	5 (5.8%)	18 (21.1%)	1.05 (0.15-3.60)

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ICU Admission	2 (2.3%)	17 (20%)	1.17 (0.27-4.14)
Respiratory Failure	3 (3.5%)	16 (18.8%)	1.70 (0.77-3.15)
Kidney Failure	2 (2.3%)	19 (22.3%)	1.60 (2.15-6.10)

Our analysis revealed that the median hospital stay for the aggressive-resuscitation group was 6 days (interquartile range: 4 to 8) and the median hospital stay for the moderate-resuscitation group was 5 days (interquartile range: 3 to 7). The relative risk [95% CI 1.25 (0.55-2.85)] for the moderate fluid resuscitation group was 8 points (IQR, 6-10) and for the aggressive resuscitation group it was 21 points (IQR, 19-23) at 12 hours, according to the full case analysis. Higher scores indicated greater symptom intensity. The relative risk [95% CI 0.25 (0.25-2.45)] after 48 hours was 3 points (IQR, 1-5) in the moderate fluid resuscitation group and 22 points (IQR, 20-24) in the vigorous resuscitation group, indicating more significantly reduced symptoms, as shown in table 3.

Table 3: Duration of Hospital Stay and Efficacy Outcomes of Study Participants

Variables	Moderate Fluid Resuscitation N (%)	Aggressive Fluid Resuscitation N (%)	Odd Ratio 95% CI N (%)	P-Value
Duration of Hospital Days (IQR)	5 (3-7)	6 (4-8)	2.55 (2.5-5.5)	0.001
Number of Days in ICU (IQR)	0%	0%	-	-
PAN-Promise Score (IQR)				
12 Hours	8 (6-10)	21 (19-23)	1.25 (0.55-2.85)	0.001
24 Hours	5 (3-7)	27 (24-30)	2.35 (1.35-5.15)	0.001
48 Hours	3 (1-5)	22 (20-24)	0.25 (0.25-2.45)	0.001
72 Hours	1 (2-4)	19 (17-21)	1.15 (2.04-6.76)	0.000
Biochemical Variables				
C-Reactive Protein mg/mL (IQR)	1.5 (2.9-5.4)	6.46 (9.3-12.5)	4.11 (2.11-5.76)	0.111
48 Hours	7.5 (3.2-3.6)	15.2 (13.5-16.5)	3.10 (1.22-6.65)	0.121
72 Hours	8.5 (4.1-4.4)	18.5 (15.4-18.4)	1.22 (3.35-7.75)	0.008

Mann-Whiteny U-test

Compared to moderate fluid resuscitation, which had an adjusted relative risk of 14.1%, aggressive fluid resuscitation (32.5%) was linked to a significantly greater incidence of fluid overload [95% CI, 5.2(3.02-6.15)]. The management of volume overload was carried out in the following ways: diuretics were used in 90% of cases, inotropes were used in 9% of cases, and decreased hydration was used in none of the cases in the aggressive-resuscitation group. No patient in the aggressive-resuscitation group required hemofiltration, although one patient had an orotracheal intubation. The median time of fluid overload was 28 hours in the aggressive resuscitation and 35 hours in the moderate resuscitation. Fluid resuscitation was associated with symptoms of fluid overload included dyspnea 14.1% in the moderate resuscitation group then aggressive resuscitation group 25.5% relative risk adjust [95% CI, (1.75(3.5-7.8)]. The sign of fluid overload also included peripheral edema 35.2% and pulmonary edema 29.4% in the aggressive resuscitation group in the patients respectively, adjust relative risk, [95%CI, 4.15(0.5-3.44), and 3.33(2.5-4.8)]. The study ended because the aggressive resuscitation group's safety outcomes were noticeably worse than those of the moderate resuscitation group, and there was no indication of a trend toward better outcomes. The data and safety monitoring board examined these results (Table 4).

Table 4: Safety Outcomes of Study Participants

Variables	Moderate Fluid Resuscitation N (%)	Aggressive Fluid Resuscitation N (%)	Odd Ratio 95% CI N (%)
Fluid Overload	12 (14.1%)	28 (32.5%)	5.2 (3.02-6.15)
Moderate Fluid Overload	11 (12.9%)	24 (28.2%)	1.05 (0.15-2.15)
Sever Fluid Overload	2 (2.3%)	25 (29.4%)	3.6 (1-9-4.7)
Symptoms of Fluid Overload	-	-	-
Dyspnea	12 (14.1%)	22 (25.5%)	1.75 (3.5-7.8)
Peripheral Edema	11 (12.9%)	30 (35.2%)	4.15 (0.5-3.44)
Pulmonary Edema	10 (11.7%)	25 (29.4%)	3.33 (2.5-4.8)
Imaginary Testing	-	-	-
Hemodynamic Testing	8 (9.4%)	26 (30.5%)	2.25 (1.50-4.75)
Heart Failure ECO Cardiogram	3 (3.5%)	27 (31.7%)	4.6 (2.43-6.23)
Pulmonary Congestion by Radiographic Evidence	10 (11.7%)	30 (35.2%)	1.55 (0.11-3.23)

Mann-Whiteny U-test

DISCUSSION

Indeed, aggressive fluid resuscitation during acute pancreatitis might raise the risk of volume overload, which can result in consequences such abdominal compartment syndrome, pulmonary edema, and congestive heart failure [13]. Aggressive fluid resuscitation in pancreatitis attempts to preserve tissue perfusion and avoid squeal such as organ failure. Volume overload can occur, nevertheless, if an excessive amount of fluid is given to the body too soon, beyond its capacity to handle it. In order to prevent volume overload, healthcare professionals must closely monitor patients undergoing vigorous fluid resuscitation and make sure that fluid delivery is balanced and altered as necessary. In order to effectively manage fluid balance, this may entail closely monitoring fluid intake and output, evaluating clinical symptoms of fluid overload such as edema and shortness of breath, and, if necessary, adopting further measures like diuretics or renal replacement therapy. In the previous literature, the effectiveness of aggressive fluid resuscitation in pancreatitis attempts to preserve tissue perfusion [14]. There are a number of considerations when comparing aggressive versus moderate fluid resuscitation for pancreatitis, including the dangers involved and how well it improves outcomes. The moderate fluid resuscitation technique is to provide the patient enough fluids at a pace that keeps their tissue perfusion at a sufficient level without overloading them. Using a higher rate of fluid administration to guarantee good tissue perfusion and

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avoid consequences like organ failure is known as the aggressive fluid resuscitation technique [15]. The degree of aggressiveness of the method and specific patient characteristics determine the risk of complications from fluid resuscitation in pancreatitis. Severe fluid resuscitation can upset the balance of electrolytes, resulting in consequences including hyponatremia (low sodium), hypernatremia (high sodium), hypokalemia (low potassium), or hyperkalemia (high potassium), which can impair heart and brain function [16]. Fluid resuscitation, especially in patients with acute pancreatitis or underlying coagulopathy, can dilute platelets and clotting factors, increasing the risk of bleeding problems or Disseminated Intravascular Coagulation (DIC). Over distribution of fluids can lead to metabolic acidosis, a disorder marked by an imbalance in the body's acid-base state that can deteriorate organ performance and patient outcomes. In the past study, the different fluid resuscitation disturbed physiological function [17]. The moderate fluid resuscitation less dangerous than aggressive fluid resuscitation. The moderate fluid resuscitation is to give the patient enough fluids at a pace that keeps their tissue perfusion intact without going overboard. Compared to intensive fluid resuscitation, moderate fluid delivery reduces the risk of abrupt changes in electrolyte balance. Aggressive fluid resuscitation often has a higher risk of gastrointestinal problems, even though moderate fluid resuscitation may still cause some fluid accumulation in the stomach. We were agreed from the previous study [18]. While aggressive resuscitation increases the risk of acute kidney injury, moderate fluid resuscitation still carries some risk, particularly for patients with pre-existing kidney problems. The severity of pancreatitis, the patient's reaction to treatment, the existence of comorbidities, and the fluid resuscitation method used are some of the variables that can affect how long a patient stayed in the hospital [19]. Let us examine the possible effects of aggressive versus moderate fluid resuscitation on the duration of hospital stay in patients with pancreatitis: Compared to patients undergoing intensive fluid resuscitation, patients receiving moderate fluid resuscitation may need to stay in the hospital for a little while longer. We used the concept of past experience (CBL workshop) also referred to as patient receive moderate fluide which was better results [20]. The moderate fluid resuscitation is to give the patient enough fluids at a rate that keeps their tissue perfusion intact without going over their fluid threshold. Although this method of treating pancreatitis might work, if complications arise or if the patient's condition does not improve as quickly, it could result in a lengthier hospital stay. Individuals undergoes vigorous fluid resuscitation might spend a little less time in the hospital than those having moderate resuscitation. The aggressive fluid resuscitation is to deliver fluids more quickly in order to maintain ideal tissue perfusion and avoid consequences like organ failure. This strategy can, in certain circumstances; result in shorter hospital stays since it efficiently manages the acute pancreatitis and decrease the risk of complications [21]. Regardless of the fluid resuscitation technique used, patients with severe pancreatitis may need to stay in the hospital longer because of the complexity of their illness and the possibility of consequences. The moderate fluid resuscitation patients were shown shorter duration of hospital as compared to aggressive fluid resuscitation. In the past study, inflammation or infected patients was stay longer [22]. The fluid resuscitation strategy, the emergence of complications such organ failure, infection, or gastrointestinal bleeding can extend hospital stays. The duration of hospital stayed and treatment response in cases of pancreatitis might be influenced by a patient's age, comorbidities, nutritional state, and other unique factors [23]. The length of hospital stay can also be influenced by individual patient characteristics, including age, comorbidities, nutritional state, and social support. Longer hospital stays may be necessary for patients with numerous comorbidities or little social support in order to receive complete care and discharge preparation. This study shows similar results previous studies [24, 25].

CONCLUSIONS

Factors like the severity of the illness, response to treatment, and the emergence of complications are more important in determining how long a patient stayed in the hospital for pancreatitis, even though the decision between aggressive and moderate fluid resuscitation may have a minor effect.

Authors Contribution

Conceptualization: AA
Methodology: NK, MS, MA, FS
Formal analysis: NK
Writing, review and editing: NK, MUH, MA, FS

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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Original Article

Evaluation of Surgical Resection and Reconstruction Outcomes in Patients with Various Histological Subtypes of Soft Tissue Sarcomas: A Prospective Cohort Analysis

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ABSTRACT

Soft-tissue sarcomas (STS) are rare, especially as histological subtypes (more than 50). Despite being more prevalent in youngsters, their prevalence rises with age. **Objective:** To analyze the outcomes of surgical resection and subsequent reconstruction in patients with different histological subtypes of soft tissue sarcomas, focusing on the complications, recurrence rates, and overall survival. **Methods:** A prospective cohort study was conducted and data were collected from 14 patients treated between 2018 to 2022 at the Department of Plastic and Reconstructive Surgery, General Hospital, Lahore. The data included a detailed analysis of patient demographics, histological subtypes, surgical techniques, and postoperative outcomes, including complications, recurrence rates, and overall survival. **Results:** Soft tissue sarcoma was identified in 2 scalps, 2 arms, 3 forearms, 2 abdominal walls, 3 lower limbs, 1 nape of the neck, and 1 lumbar area. Two patients received neoadjuvant radiation and one chemotherapy. The tumors were 5–17.5 cm wide. Pleomorphic sarcoma was the most prevalent STS subtype, followed by liposarcoma and leiomyosarcoma in histology. This six-patient technique employed Latissimus dorsi, radial forearms, musculocutaneous gastrocnemius, free anterior lateral thigh (ALT) muscles, and year-end median. Complications occurred in 3 out of 14 patients who received flap reconstruction (complete flap failure in one patient, seroma in one patient, infection in one patient). The recurrence rate was 4 (28.6%) and survival rate was 13 (92.9%). **Conclusions:** This study concluded that R0 resection followed by immediate soft tissue reconstruction has helped in the management of such complex cases in terms of less complications and recurrence rate.

INTRODUCTION

Soft tissue sarcomas (STS) are an aggressive subtype of solid tumors that affect 1% of adults and 7% of children, with an annual incidence of 5 cases per 100,000 individuals [1]. A total of fifty distinct histological subtypes have been identified for STS. The most common STS in children is rhabdomyosarcoma, but undifferentiated pleomorphic sarcoma is more common in adults [2, 3]. Cervical sarcomas often present as soft, painless lumps. Both the patient and the clinician may fail to recognize the significance of swellings when the underlying reason is unclear. A much larger tumor is typically visible when a patient first visits the outpatient clinic after a delay in STS detection. Restoring these defects is a significant task for the plastic surgeon since complex abnormalities can result from the tumor's size and its connection with nearby tissues. Though the majority of STS are found on the limbs and trunk, a few may be seen in the retroperitoneal area [4]. When individuals with STS experience metastasis to the lungs, there's a good chance that the cancer will return locally. The main places for STS therapy should be tertiary care centers with specialized multidisciplinary teams of radiologists, pathologists, oncologists, and ablative and

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reconstructive surgeons [5, 6]. To get the best possible local therapy, it is essential to have sufficient resection margins as positive margins on surgical excision are the most important predictor of local recurrence [7]. The problem of attaining negative margins while keeping function is raised by the fact that STS typically occur near to or are principally associated with neurovascular systems. Results from studies using adjuvant and neoadjuvant radiation to treat cancer have demonstrated encouraging rates of limb salvage and sufficient resection margins. On the other hand, a lot of these removals are tricky and could need a lot of vascular repair or dissection [8]. There is a rare and difficult-to-treat subset of malignant tumors known as soft tissue sarcomas (STSs). These tumors are mesenchymal in origin and can develop anywhere in the body. Approximately half to two-thirds of STSs affect the extremities, which is why the name "extendity STSs" (ESTSs). As a therapy technique, surgery with negative margins which typically required amputation has provided the backbone [9, 10]. Disabilities and impairments that patients experience after undergoing amputation for ESTS therapy have caused significant distress due to the diminished level of functionality they experience. Results from a prior randomized prospective research comparing limb-sparing surgery with radiation to amputation for patients with ESTS found no change in OS or disease-free survival (DFS) [11]. Surgery for the treatment of ESTS is typically performed in conjunction with radiation, either before, during, or after the operation, to preserve the best possible structure and function of the limbs and joints. When treating non-metastatic sarcoma, it is crucial to remove the tumor completely while maintaining an adequate margin of healthy tissue. In STS, tumor resection with R0 margins is considered the gold standard [7]. By definition, "R0" resection involves removing the tumor's margins. As an alternative to the traditional practice of amputation, modern clinical practice includes limb-sparing resections for the majority of patients, all while maintaining sufficient survival rates [8]. Patients whose cancer has spread to other parts of the body may have adjuvant radiotherapy and chemotherapy as part of their treatments [9].

This study aimed to demonstrate how the tumor board's collective knowledge and the outcomes of interdisciplinary collaboration are critical to attaining both local disease management and disease-free survival.

METHODS

A prospective cohort analysis of all patients who underwent interdisciplinary surgical therapy for soft-tissue sarcomas at Lahore General Hospital, Lahore over a period of 5 years from 2018 to 2022 after getting approval with reference (111-2017). Fourteen individuals were considered for inclusion and patient's consent was obtained before study. Because the needed sample size was 14 patients, the estimation of the sample size was based on the prevalence of 18%, the margin of error was 10%, and the confidence interval was 95%. The non-probability purposive sampling approach was modified to fit the situation. Histologically verified STS diagnosis and therapy at our center were the inclusion criteria for this investigation. Patient demographics (median age and sex), cancer treatment modalities (neoadjuvant radiotherapy, neoadjuvant chemotherapy, adjuvant radiotherapy, and adjuvant chemotherapy), tumor characteristics (tumor location, tumor size, histological subtypes), reconstructive methods utilized post-tumor ablation, and post-operative follow-up were among the many pieces of information drawn from electronic health records. All the patients with a clinical history of pain and swelling in any region of the body with the size of the swelling equal to or greater than 5cm, progressive increase in the size of the swelling, or solid masses originating in deep subfascial planes were first investigated with X-ray to rule out bony tumors followed by MRI with contrast. The conventional method of diagnosis, after appropriate imaging evaluation, was doing several core needle biopsies (with needles >16G). For the superficial lesions, nevertheless, an incisional biopsy was performed. The senior surgeons were the ones who conducted the biopsies. The plan called for the last operation to remove the scar and the biopsy route without causing any harm. The research covered all individuals whose tumors were found to be soft tissue sarcoma. When the first diagnosis was made outside of our clinic, we always sought a second opinion from a pathologist. The American Joint Committee on Cancer (AJCC) approach was used for staging, which involved recording the tumor's location, size, and depth relative to the muscle fascia. Staging with the AJCC does not apply to certain types of cancer, such as angiosarcoma and Dermatofibrosarcoma Protuberans (DFSP). All such cases were then discussed in a tumor board meeting together with the pathologist, radiologist, ablative surgeon, plastic surgeon, and clinical oncologist. The management plan regarding neoadjuvant chemo/radiotherapy and excision of STS followed by reconstruction was delineated and documented. The recommendations of the tumor board were explained and thoroughly discussed with the patient including all surgical options, the pros and cons of each option, and the role of neo-adjuvant or adjuvant chemo/radiotherapy. Patients with Stage I-III tumors were planned for surgery however Stage IV tumors were not operated and were sent for radiation. The tumor resection was performed by the ablative surgeon (general surgeon/neurosurgeon and/or

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orthopedic surgeon). The R0 resection margins were obtained by achieving histopathologically negative margins on frozen section. Eight to ten tissue fragments were harvested from the tumor bed for the frozen section. After confirming margin clearance, the immediate reconstruction was carried out by the plastic surgery department. The radiation therapy was employed as a part of the standard treatment protocol in all tumors > 5cm in maximum dimension, high-grade tumor histology, and deeply located STS following primary wound healing in 3-4 weeks. Radiation therapy was not considered in cases where a true compartmental resection of the tumor-containing compartment was done. Although it is not typically recommended for adult-type soft tissue sarcomas, high-risk individuals may be offered adjuvant chemotherapy as an alternative therapeutic option. During the first two to three years, patients were monitored every three to four months. After that, biannually until the fifth year, and then annually after that. Outcomes of surgical resection and subsequent reconstruction in patients with different histological subtypes of soft tissue sarcomas, focusing on the complications, recurrence rates, and overall survival. SPSS version 23.0 was used for statistical analyses. Frequencies and percentages were used for categorical variables.

RESULTS

The median age of the patients was 42.1 years, where 8 patients were male while 6 patients were female. Among all, 11 patients were married and 3 were non married. Majority of the cases 9 had rural residency and 10 cases had poor socioeconomic status. Neoadjuvant radiation was administered to two patients, whereas one patient underwent neoadjuvant chemotherapy. Adjuvant radiation was given to nine individuals and adjuvant chemotherapy to two patients after surgery. The tumors ranged in size from 5 cm to 17.5 cm round (Table 1).

Table 1: Demographics of the Presented Cases

Variables	Frequency/Percentage
Median Age (Years)	42.1
Gender	
Male	8 (57.1%)
Female	6 (42.9%)
Marital Status	
Married	11 (78.6%)
Unmarried	3 (21.4%)
Residency	
Urban	5 (35.7%)
Rural	9 (64.3%)
Socio-economic status	
Poor	10 (71.4%)
Middle/High	4 (28.6%)
Techniques	
Neoadjuvant Radiation	2 (14.3%)
Neoadjuvant Chemotherapy	1 (7.1%)
Adjuvant Radiation	9 (64.3%)
Adjuvant Chemotherapy	2 (14.3%)
Mean Size of Tumor (cm)	11.4

It was found that 2 patients had soft tissue sarcoma of the scalp, and 02 of the arms, 03 patients had sarcoma of the forearm, 02 had abdominal wall sarcoma, 03 patients had lower limb sarcoma while 1 patient had STS at the nape of the neck, and 1 had STS of the lumbar area. Histopathological examination revealed that pleomorphic sarcoma, liposarcoma, and leiomyosarcoma were the most prevalent subtypes of STS. Spindle cell sarcoma, chondrosarcoma, synovial sarcoma, and dermatofibrosarcoma protuberans were among the other subtypes that were identified. Unclassified sarcoma was the diagnosis for one patient's sample. The most frequently used flap was Latissimus dorsi muscle in 6 patients, Radial forearm free flap in 3patients, vertical rectus abdominis myocutaneous (VRAM) flap (2 patients), while 1 patient's defect was reconstructed using a free anterior lateral thigh (ALT) flap. A musculocutaneous gastrocnemius flap was used for reconstruction in 2 patients (Table 2).

Table 2: Results Showing Tumor Location, Type, and Reconstruction Done

Area of Tumor	No. of cases	Nature of Tumor	Frequency/Percentage
Scalp	2	Dermatofibrosarcoma protuberans	Free Latissimus Dorsi Flap
		Pleomorphic sarcoma	Free Latissimus Dorsi Flap
Arm	2	Synovial sarcoma	Free Radial Forearm Flap
		Pleomorphic sarcoma	Free Radial Forearm Flap
Forearm	3	Spindle cell sarcoma	Free Latissimus Dorsi Flap
		Liposarcoma	Free Radial Forearm Flap
		Pleomorphic sarcoma	Free Anterolateral thigh Flap
Nape of Neck	1	Pleomorphic sarcoma	Pedicled Latissimus Dorsi Flap
Lumbar Area	1	Leiomyosarcoma	Pedicled Latissimus Dorsi Flap
Abdominal Wall	2	Leiomyosarcoma	Vertical Rectus Abdominis Flap
		Liposarcoma	Vertical Rectus Abdominis Flap
Lower Limb	3	Liposarcoma	Pedicled Gastrocnemius Flap

The median follow-up was 12 months. Complications occurred in 3 out of 14 patients who received flap reconstruction (complete flap failure in one patient, seroma in one patient, infection in one patient). Recurrence rate was 4 (28.6%) and survival rate was 13 (92.9%) (Table 3).

Table 3: Outcomes Among All Cases After Therapy

Variables	Frequency/Percentage
Complications	
Flap Failure	1 (7.1%)

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Seroma	1(7.1%)
Infection	1(7.1%)
Recurrence Rate	
Yes	4(28.6%)
No	10(71.4%)
Survival Rate	
Yes	13(92.9%)
No	1(7.1%)

After achieving R0 tumor resection under frozen section control, all patients required either a pedicled or a free flap for resurfacing the complex soft tissue defects. One complete free LAD flap loss was encountered for scalp reconstruction, for which a local scalp flap was performed. The other patient with seroma formation was dealt with ultrasound-guided aspiration while for one patient with infections, culture-specific intravenous antibiotics were administered for a period of 1 week.

Once the wounds healed in 3-4 weeks, patients were referred to medical oncologist for adjuvant radiotherapy/ chemotherapy. Secondary reconstructions for functional recovery of limbs included nerve grafting in 2 patients and tendon transfers in 2 patients(figure 1).

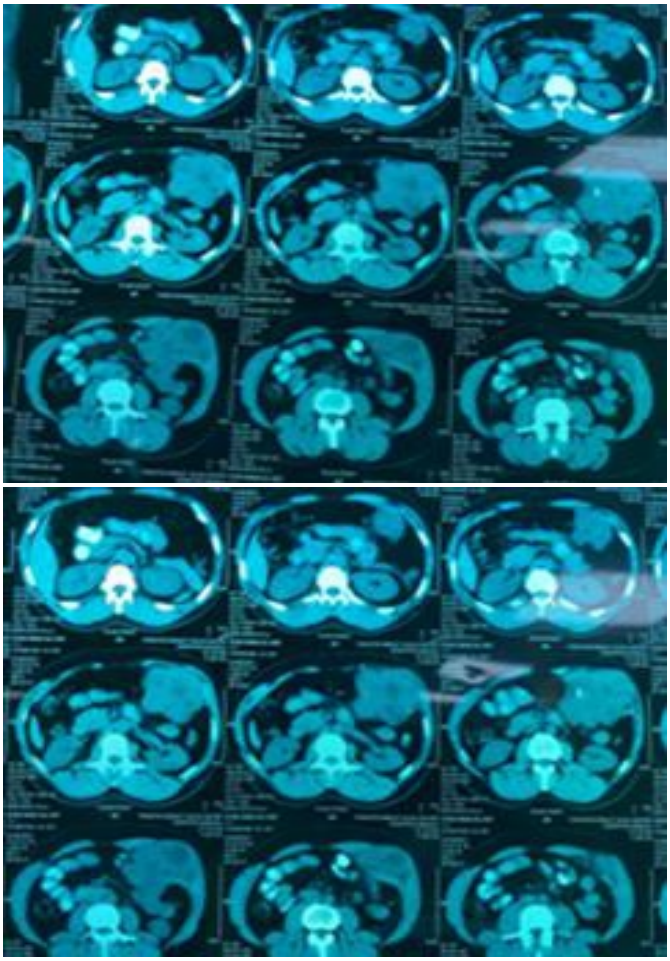

Figure 1: MRI Scans of Tumors

DISCUSSION

An early interdisciplinary strategy is necessary to prepare every patient receiving therapy for soft tissue sarcoma for excision and reconstruction. Urgent referral to a specialized sarcoma centre is required for all patients presenting with a soft-tissue tumor of unknown origin suspected of being sarcoma. When diagnosing STS, the gold standard diagnostic imaging method is magnetic resonance imaging (MRI) using diffusion-weighted imaging. Necrotic areas, fluctuating T2 signal intensities, and peritumoral postcontrast enhancement are hallmarks of high-grade (G3) tumors [10]. Also, MR can show you how big the tumor is, how far it has invaded if it has spread to other tissues, and how the lymph nodes are doing. There are three options for mass size and depth-based biopsy: core needle, incisional, and excisional. Excisional biopsies are a good choice for superficial masses with a diameter of 3 cm or less than 11 cm. With many passes and a gauge size of 16, core needle biopsy can detect STS subtypes with less problems compared to incisional biopsy, according to current research. Histological findings can differ and diagnostic errors are common since STS contains many distinct kinds of tumors. Because of the variety of possible STS diagnoses, only a highly trained sarcoma pathologist can be trusted with the task of analyzing biopsy results [11]. Medical oncologists, radiologists, pathologists, radiotherapists, ablative and plastic surgeons, and members of a multidisciplinary tumor board should convene to assess treatment regimens. Neoadjuvant therapies include but are not limited to, chemotherapy and radiation therapy. It is essential to have a multidisciplinary team look at patients before, during, and after surgery for a proper diagnosis. To reduce the chance of local recurrence, radiation is an important part of STS therapy regimens for Stages II, III, and IV [12, 13]. Even though no new evidence has emerged to support the claim that adjuvant or neoadjuvant radiation methods are better, the debate about how many despite the increased risk of acute wound complications and flap failure associated with neoadjuvant radiation, it does provide certain advantages, such as decreased edema and joint stiffness as well as lower fibrosis, in long-term follow-ups compared to adjuvant radiotherapy. Systemic chemotherapy is an effective treatment for advanced or metastatic tumors of the skin [14, 15]. Conventional cytotoxic chemotherapy has relied on anthracycline (doxorubicin) and ifosfamide derivatives [16, 17]. However, new experiments have cast doubt on their effectiveness owing to severe toxicity and poor treatment results. New targeted medicines, such as trabectedin for liposarcoma and leiomyosarcoma, have been developed as a result of discoveries in molecular etiology [18, 19]. Extensive excision is necessary after histological confirmation of STS to guarantee margins free of tumors as small as microscopic particles. Inadequate

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marginal resections cannot ensure R0 resection. Although amputation of the affected limb was once the norm for sarcoma treatment, recent data shows that R0 resection can provide the same or better long-term outcomes without the limb being amputated. By carefully removing the tumor while leaving intact surrounding tissue, a wide resection ideally makes the tumor undetectable. Radical tumor removal with neighboring muscle tissue and nerves preserved or functional deficiencies repaired by additional treatments are examples of how preservation of function is prioritized [20]. It is critical to immediately use vascularised soft tissue for defect restoration following R0 resection. Furthermore, it is not necessary to remove the whole compartment if the tumor does not extend into or through the muscle's origin or insertion. When combined with aggressive tumor removal, preserving function by removing nearby muscle tissue around the tumor was just as effective as removing the entire compartment in terms of long-term survival. To avoid damaging surrounding nerves due to inadequate tumor removal, epineural dissection is used. Although amputation of the leg is not always necessary, tumor infiltration of arteries and/or nerves necessitates resection and, if necessary, regeneration of these tissues [21]. When a tumor has progressed too far when a patient is too elderly or too sick to undergo complex repair, or in other severe cases, amputation of a limb may be required. Surgical treatment can be broadly classified as oncological excision, bone and soft tissue repair, and nerve and vascular or functional reconstruction [22]. The wide range of flaps used for reconstruction demonstrates the difficulty of surgically treating STS in the limbs [23]. Before choosing the best flap, it is important to study the location, diameter, depth, and nearby vessels. Surgeon discretion dictates whether reconstruction occurs simultaneously with tumor removal or after histological confirmation of an R0 resection. A two-step procedure can minimize complications caused by positive margins after the initial resection and allows for more exact planning of the required repair, but a one-step procedure has the benefits of less time spent in the hospital and faster recovery. In our study Complications occurred in 3 out of 14 patients who received flap reconstruction (complete flap failure in one patient, seroma in one patient, infection in one patient). The recurrence rate was 4 (28.6%) and the survival rate was 13 (92.9%). The results were in line with the previous research [17-20]. However, when problems are detected, a two-step method is necessary. Recent research has shown that NPWT, or a vacuum-assisted closure regimen, can lessen the occurrence of wound problems during the excision to the reconstruction process [24]. Before creating surgical procedures for each patient, it is crucial to evaluate the vascular status in the limbs, especially around the tumor [25]. Furthermore, to further enhance reconstruction safety and prevent flap loss, intraoperative imaging using indocyanine green angiography or blood flow analysis is an option [26]. It may be possible to avoid ligating the vessels during resection and avoid leaving no recipient vasculature to support the anastomosis of free flap vessels if a one-step approach is considered in cases where free flap reconstruction is necessary but the only large vessels in the tumor region are invading the tumor [27]. After the tumor is removed, there are no longer any recipient vessels. The recipient vasculature can be built as an arteriovenous loop for the rest of the therapy in a one- or two-step method. The ALT flap and the VRAM flap are two examples of pedicled flaps that may be used to conceal defects; they are commonly used on the anterior lateral thigh and in the groin [28]. These flaps can also be used in a free-flap fashion [29]. For greater anomalies, a combination of latissimus dorsi and para scapular or serratus anterior muscle flaps might be used to augment the flap area. Although nerve grafts can help restore large nerves that have been amputated after surgery, tendon transfers are often required for optimal motor recovery. Performing functional muscle transfers is also a common procedure. There is reason to question the study's validity due to the tiny sample size. The observed trends highlight the importance of early patient assessment for rapid reconstructive surgery following Ro resection; however, more study is required to confirm these results. The absence of an internal control group is only one of several limitations that must be acknowledged in this study. In addition, additional subgroup analysis is not feasible due to the series' short size and heterogeneity. Although our Institute is a national reference center, the amount of samples and diagnostic heterogeneity are correlated with the rarity of individual tumors.

CONCLUSIONS

It was concluded that R0 resection followed by immediate soft tissue reconstruction has helped in the management of such complex cases in terms of less complications and recurrence rate. Free flaps have revolutionized the entire management of soft tissue sarcomas as large defects can be reconstructed immediately. The multimodality approach remains the standard of care in such complex cases.

Authors Contribution

Conceptualization: SF, RA
Methodology: SI, MI
Formal analysis: MN, MAA
Writing-review and editing: SF, RA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Systematic Review

Diagnostic and Prognostic Potential of Biochemical and Hematological Markers in Tobacco Users with Oral Pre-Cancer Lesions

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ABSTRACT

Oral Pre-Cancer Lesions (OPLs) including leukoplakia, erythroplakia, and submucous fibrosis denote biochemical and histopathologically altered changes in the oral mucosa marked by subcellular and structural anomalies evocating of potential for a malignant transformation, which is primarily caused by tobacco exposure. Early diagnosis is of paramount importance to halt the progression of premalignant lesions to high-grade dysplasia and even oral cancer. **Objective:** To find the diagnostic and prognostic potential of biochemical and haematological markers in Tobacco Users (TU) with OPL. **Methods:** PRISMA guidelines were followed to perform this systematic review. After retrieving 170 epidemiological studies published from 2013 to 2023, through multiple databases (PubMed, Google Scholar, Sci-hub, and Science Direct), 21 were included to determine the potential of biochemical and haematological markers in risk stratification and early detection of OPL. **Results:** According to the following systematic review, extracted data showed specific biochemical and haematological indicators that could serve as markers in risk stratification and early detection of OPL. The OPL group exhibited significantly higher levels of biochemical markers IL-6, IL-8, TNF-α, HCC-1, PF-4, FRR, TP, MDA, MMP-12, and Ceruloplasmin and hematological markers NLR, PLR, CRP, ESR, WBC, and low Hb as compared to the control group. Following risk stratification, a group with older age, tobacco association with OPL, and elevated levels of markers were categorised as a higher-risk group. **Conclusions:** The biochemical and haematological markers are potential promising markers in the early detection of OPL from malignant lesions with diagnostic and prognostic significance.

INTRODUCTION

Oral Premalignant Lesions (OPLs) of the oral cavity span a diverse array of pathology. OPL is defined as a morphologically altered or abnormal change in the tissue of the oral mucosa that exhibits potential for malignant transformation [1]. It was proposed as an Oral Potentially Malignant Disorder (OPMD) by the World Health Organization in 2005 [2]. These precancerous lesions include leukoplakia, submucous fibrosis and erythroplakia [3]. The oral cavity is lined with stratified squamous epithelium which is sensitive to potential carcinogens [2]. Epithelium anomaly accompanied by exposure to carcinogens such as tobacco, alcohol, Human Papillomavirus (HPV) and betel nut might produce a cellular microenvironment that leads to the formation of dysplastic epithelium. It clinically manifests as premalignant oral lesions, leukoplakia, lichen planus, erythroplakia and has

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diverse rates of progression to carcinoma. The presence of dysplastic epithelium in any of these entities underscores the necessity of histopathological assessment [4, 5]. OPL affect 1.5% to 4.5% of the global population with a higher prevalence in men compared to women [6 7]. The incidence was higher in Asian, South American and Caribbean populations, reflecting geographical variations attributable to different rates of alcohol and tobacco consumption [2]. Out of every 100th cancer case reported worldwide, 17 to 35 are of oral cancers. The Malignant Transformation Rate (MTR) of OPLs accounts for 0.7% to 2. 9% annually [8, 9]. Globally, HPV is also a contributing factors for oral premalignant lesions [10]. However, tobacco use either smokeless or smoking, has emerged as one of the most significant factors among the various contributors to the development of all types of OPL and is composed of alkaloid nicotine and other harmful substances which are deadly carcinogens and toxic [9, 11, 12]. Leukoplakia develops as white patches or plaques on the oral mucosa; erythroplakia materializes as red patches; clinical manifestations of OSMF associated with fibrotic changes in the oral submucous lead to restricted mouth opening and chewing [13]. The progression of premalignant lesions to malignant oral cancer such as Oral Squamous Cell Carcinoma (OSCC) is accompanied by several stages, varying types of dysplasia and clinically prominent variable states of the oral mucosa [14, 15]. The malignant transformation rate of OPL to OSCC varied based on factors, population, gender, habits and dysplasia severity. Effective management and diagnosis of premalignant lesions at early stages aids in halting the progression to oral cancer and is a preeminent priority to reduce mortality and morbidity [16]. Histopathological moderate to severe degree of Oral Epithelial Dysplasia (OED) is a conventionally utilized cue to determine the risk of malignant transformation by inspection and palpation. However, this histologic method is sparse and results in inaccurate outcomes. As a substantial number of lesions that lack dysplastic alternation microscopically before advancement into oral cancer, OED and early OSCC appear as minor lesions of normal mucosa, whereas Leukoplakia and leukoedema are clinically similar to high-risk OPL It indicates that the traditional approach of oral examination performed by an oral oncologist is unable to precisely detect and distinguish OED, early OSCC, other lesions and classify OPL as high risk or low risk and lead to diagnosis at advanced disease stages [17, 18]. The non-invasive approach involves markers that can identify premalignant oral lesions and may be effective for proactive intervention in patient groups at high risk [19]. Therefore, biochemical and haematological markers show significant potential in mitigating diagnosis limitations and could serve as gold standards [20]. The biochemical markers include proinflammatory cytokine Matrix Metalloproteinase (MMP) Lactate Dehydrogenase (LDH) that can detect early cellular changes and inflammation associated with OPL [21-23]. Hematological markers include Complete Blood Count (CBC), differential count (DC), Neutrophil to Lymphocyte Ratio (NLR) and Erythrocyte Sedimentation Rate (ESR) which can indicate cellular dysregulation inflammation abnormalities in blood cell count associated with OPL [24]. To date, there are limited comprehensive studies on these markers. Therefore, this study is conducted with the objective of finding the diagnostic and prognostic potential of biochemical and haematological markers in Tobacco Users (TU) with OPL.

The systematic review aimed to augment existing literature by providing a comprehensive examination to assess the potential of biochemical and hematological markers in risk stratification and early detection of OPL in TU that would help clinicians and researchers to optimize their approach to the early detection of OPL and to arrest progression into oral cancer.

METHODS

Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines were followed to perform this systematic review. The data for the last (omit this word) OMITTED ten years 2014-2023 was collected using several databases (PubMed, Google Scholar, Sci-hub and Science Direct) using Boolean logic "AND" and "OR" and searching through Medical Subject Headings (MeSH Terms) and keywords. Different terminologies were used to explore the literature "Potential" "Biochemical markers" and "Hematological markers" combined with "Premalignant oral lesions", A total of 170 articles were retrieved from the included databases. Out of all these studies, 21 articles were considered eligible after applying inclusion/exclusion criteria and deleting the duplicates and irrelevant articles (Figure 1). To determine the association of tobacco with OPL, the statistical test of Chi-square using Microsoft Excel 365 was applied to 9 studies included based on homogeneity in data. Other studies were excluded due to variances in characteristics like methodologies. With degree of freedom as 1 and a P-value less than 0.05 was used to determine the significant ($p<0.05$) association was found between TU and the group of subjects with OPL as compared to the control group (CL). The risk stratification was performed based on TU association with OPL or OPM, Age, biochemical and haemotological markers level, and tobacco type and placed into different risk groups (Higher Risk Group, Moderate Risk Group, and Lower Risk Group). The group with OPL and OML with the use of tobacco and elevated levels of biochemical and hematological markers

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was identified as a higher risk group, a group with TU considered as a moderate risk group and CL, non-tobacco user and without OPL designated low-risk group. To assess specificity, the studies chose a reference standard through histopathological examination like a biopsy, blood tests, or saliva tests, and cut-off values are established for each marker based on existing literature. They involved CL groups without OPL and evaluated multiple markers in combination. The endpoints of the study included potential and levels of biochemical and haematological markers, and discrimination between precancerous and cancerous lesions. To make sure that the respective marker was against the cancer and not against any other inflammatory disease or cause, studies generally included healthy control groups without oral lesions and no evidence of inflammation in the mouth. This allowed comparing marker levels between the OPL group and both control groups which differentiated markers specifically elevated in OPLs from those that might be elevated due to general inflammation. Furthermore, studies reviewed existing literature on potential markers. Established markers with documented associations with OPL progression provided a stronger foundation for further investigation. In figure 1, PRISMA flowchart depicting the study selection process for determining the potential of biochemical and haematological markers in risk stratification and early detection of Oral Pre-Cancer Lesions in tobacco users.

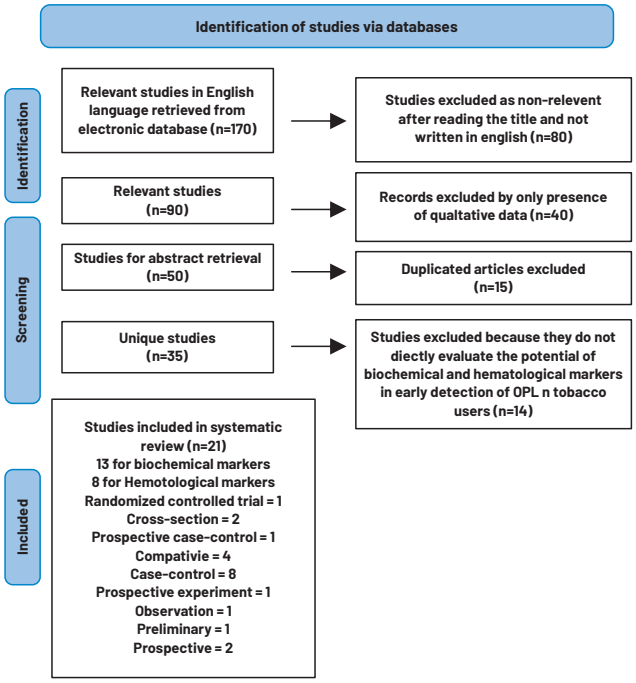

Figure 1: Prisma Flowchart Depicting the Study Selection Process

RESULTS

The available data evaluates the potential of biochemical and hematological markers in risk stratification and early detection of OPL. In the table 1, all of the identified studies determine the potential of biochemical markers in risk stratification and early detection of OPL by comparing the patients who consumed tobacco with OPL and malignant lesions with CL [21-34]. The endpoints of the study included potential and levels of biochemical markers, and discrimination between precancerous and cancerous lesions. The pro-inflammatory cytokines IL-6, IL-8, TNF-α, HCC-1, PF-4, TNF-α and IL-6 and combined Proteomics, IL-8, IL 1β, transcriptomic, DUSP1 distinguished the OPL from malignant lesions and serve as potential markers in early detection of OPL and have diagnostic and prognostic significance [21, 27, 30]. Punyani et al., reported IL-8 alone as non-conclusive for OPL detection whereas IL-6 was found as a potential marker [29, 32]. FRR and TP are potential biochemical salivary markers for OPL with a sensitivity and specificity of 54.4% to 82.3% [26]. Nimbal *et al.*, reported low levels of GSH and serum albumin in TU, and TU with OPL as compared to CL [33]. The risk stratification was done considering the level of biochemical markers. They were correlated with the TU and presence of OPL or OPM. The group with OPL and OML with the use of tobacco and elevated levels of biochemical markers was identified as a higher risk group, a group with TU considered as a moderate risk group and CL, Non-TU and without OPL designated low-risk group [21-34]. Abbreviations: OPL: Oral Premalignant Lesions; CL: Control; Tu: Tobacco User; PM: Premalignant; Lk: leukoplakia OSF: Oral Submucous Fibrosis; OL: Oral Lichen; LDA: Lactate Dehydrogenase; IL: Interleukin; ADA: Adenosine Deaminase; FRR: Ferritin; TP: Total Protein; MMP; Matrix Metalloproteinase; GSH: Glutathione; MDA: Malondialdehyde; TNF: Tumor Necrosis Factor ; OSCC: Oral Squamous Cell Carcinoma ; PF4: Platelet Factor; HCC-1: Human CC Chemokine; HRG: Higher Risk Group; MRG: Moderate Risk Group; LRG: Lower Risk Group; SLT: Smokeless Tobacco.

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Table 1: Summary of Biochemical Markers and their Outcomes in risk Stratification and Early Detection of Premalignant Oral Lesions Human Samples

S.No	Groups	OPL	Tobacco User/PM	Sample (All Studies on Humans)	Chemical Markers	Outcomes	Risk Stratification	Study	Reference
1	CL Subjects (St): 26 TU St: 26 TU+OPL St: 26	PM	yes	Saliva	LDH	Increased LDH levels in TU with OPL compared to TU alone and CL LDH as potential /promising marker in early stages of PM progression to oral cancer	Subjects with OPML and TU are classified as high -risk group (HRG), TU only as moderate-risk (MRG), and CL as low-risk group (LRG)	Comparative	Javaraiah *et al* (2020)[23]
2	OPL St: 100 OSCC St: 100 CL St: 100	PM	yes	Saliva	TNF-α	Increased TNF-α levels in TU with OPL compared to TU alone and CL Potential /promising marker in detection of OPML	HRG: OSCC subjects LRG: OPML and CL	Prospective experimental	Krishnan *et al* (2020)[25]
3	OPML St: 33 OSCC St: 33 CL St: 33	OL	9	Saliva	IL-1α,IL-6, IL-8,IP-10 MCP-1, TNF-α, HCC-1, and PF-4	IL-6,IL-8,TNF-α, HCC-1, and PF-4 were discriminated OL, OSCC, and CL/serves as potential markers in early detection No correlation was found among tobacco	HRG: OL subjects LRG: CL subjects	Casecontrol	Dikova *et al* (2021)[21]
4	OPL St: 57 CL St: 32	OL	9.90%	Saliva	ADA,FRR, TP	FRR and TP are potential salivary markers for OPL with sensitivity and specificity 54.4% to 82.3%	HRG: OPL subjects LRG: OSCC and CL subjects	Casecontrol	López-Jornet *et al* (2023)[26]
5	OPL St: 60 OSCC St: 60 CL St: 60	PM	58/96.7%	Saliva	Proteomics, IL-8, IL 1β, transcrip-tomic, DUSP1	Combined Proteomics and transcriptomic markers discriminated OPL and OSCC and from CL/Potential for OPML detection Tobacco consumption was higher in the OPL group	HRG: OPL subjects LRG: OSCC and CL subjects	Casecontrol	Gleber-Netto *et al* (2016)[27]
6	OPL St: 30 OSCC St: 30 CL St: 30	Lk	17/56.7%	Saliva	TNF-α	Increased TNF-α levels in OSCC compared to OPL and CL TNF-α can be used as a marker for predicting premalignant oral lesions and distinguishing premalignant from malignant oral cancer	HRG: OPL subjects LRG: OSCC and CL subjects	Comparative	Ameena *et al* (2019)[28]
7	OPL St: 25 OSCC St: 25 CL St: 25	PM	25	Saliva	IL-8	IL-8 was found as non-conclusive for premalignant lesions /requires further research with large sample sizes	HRG: OPL subjects LRG: OSCC and CL subjects	Preliminary	Punyani *et al* (2013)[29]
8	OPL St: 19 OSCC St: 19 CL St: 19	PM	NR	Saliva	TNF-α and IL-6	Increased TNF-α and IL-6 levels in OSCC compared to OPL and CL Discriminated OSCC, OPL from CL /have diagnostic and prognostic significance	HRG: OPL subjects LRG: OSCC and CL subjects	Casecontrol	Jureti *et al* (2013)[30]
9	OPL St: 30 CL St: 30	PM	19	Blood	MDA	Increased MDA levels in OPL compared to CL Potential biomarker for early detection	HRG: OPL subjects LRG: CL subjects	Casecontrol	Mohideen *et al* (2021)[31]
10	OSF St: 30 OSCC St: 30 CL St: 30	OSF	19	Blood	MDA	OSCC>OSF>CL Increased MMP 12 levels in OSCC compared to OSF and CL MMP-12 markers serve as a non-invasive early diagnostic tool for premalignant oral lesions	HRG: OSF subjects LRG: OSCC and CL subjects	Casecontrol	Saleem *et al* (2019)[22]
11	OPL St: 100 OSCC St: 100 CL St:100	PM	100	Saliva	IL-6	Proinflammatory cytokines IL-6 have diagnostic and prognostic significance	HRG: OPL subjects LRG: OSCC and CL	Casecontrol	Dineshkumar *et al* (2016)[32]

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12	CL St: 60 TU St: 60 TU+OPL St: 60 TU+OML: St: 60	PM	yes/60	Blood	GSH/Serum albumin/TP	GSH and serum albumin decrease with increased use of tobacco TP was found as a weak marker/GSH and serum albumin were reliable markers	HRG: TU and OPL subjects MRG: TU and OML subjects LRG: TU and CL subjects	Cross-sectional	Nimbal *et al* (2024)[33]]
13	Lk St: 25 OSF St: 25 OSCC St: 25 CL St:25	Lk/ OSF	Yes	Sera	Cerulo-plasmin	Higher levels in three groups compared to CL. Potential markers for OPML and OSCC An association was found between gutkha and smoking tobacco	HRG: Lk and OSF subjects LRG: CL	Observational	Patil *et al* (2021)[34]

In the table 2, all of the identified studies evaluate the potential of hematological markers in risk stratification and early detection of OPL by comparing the patients who consumed tobacco with OPL and malignant lesions with CL [24, 33, 35, 36-41]. The endpoints of the study included potential and levels of hematological markers, and discrimination between precancerous and cancerous lesions. Vankadara *et al.*, and Salema *et al.*, reported CRP as a potential marker used to discriminate and gauge premalignant lesions and malignant transformation [35, 36]. The hematological markers NLR with sensitivity and specificity of 92%, PLR, HB, ESR, PLC DLC, and WBC were found as valuable prognostic indicators for OPL [41]. However, further research is required to claim these as reliable diagnostic markers [24, 33, 35-40]. The risk stratification is done considering the level of hematological markers. The group with premalignant and malignant lesions with the use of tobacco and elevated levels of CRP, NLR, PLR, ESR, and WBC was identified higher risk group, a TU group considered as a moderate risk group and CL, Non-TU and without OPL deemed low-risk group [24, 33, 35-41]. Abbreviations: OPL: Oral Premalignant Lesions; CL: Control; Tu: Tobacco User; PM: Premalignant; CRP: C-Reactive Protein; ESR: Erythrocyte Sedimentation Rate; NLR: Neutrophil-Lymphocyte Ratio; PLC: Platelets Count; Hb; Hemoglobin; TLC: T-Lymphocytes Count; WBC: White Blood Cells; PLR: Platelet-To-Lymphocyte Ratio; OML: Oral Malignant Lesions; HRG: Higher Risk Group; MRG: Moderate Risk Group; LRG: Lower Risk Group Statistical Chi-square test and Risk stratification. In Table 3 attached as a supplementary file, nine studies were specifically included based on homogeneity in data as the studies shared similar characteristics according to the chi-square principle [21, 22, 26, 27, 30-34]. Other studies were excluded as including studies with different characteristics like methodologies could lead to misleading results. Statistical test Chi-square was applied using 'Microsoft Excel' to determine the association of tobacco with oral premalignant lesions. Overall, a statistically significant p value < 0.05 (with D.F =1) association was found between TU and the group of patients with OPL as compared to the CL group, as individual analysis might lead to inconclusive or weak results due to limited data [22, 26, 27, 31-34]. A non-significant association was observed in the two studies possibly due to the small sample size or the influence of confounding factors [21, 30]. The risk stratification was done based on tobacco use association with OPL, Age, biochemical markers level, and tobacco type. All types of tobacco correlated with increased risk of OPL in which smoking is common. The group of patients with old age TU association with OPL elevated level of biochemical markers was categorized as a higher risk group, whereas as CL group younger age than the older group and without association of tobacco with OPL and low level of biochemical markers was deemed low risk group [21, 22, 26, 27, 30-34] (Table 3: Supplementary information).

Table 2: Summary of Hematological Markers and their Outcomes in Risk Stratification and Early Detection of Premalignant Oral Lesions

S.No	Groups	OPML	Tobacco User/PM	Sample	Hematological Markers	Outcomes	Risk Stratification	Study	Reference
1	OPML Subjects (St): 30 CL St: 30	PM	Yes	Blood	CRP	Increased CRP levels in OPL compared to CL subjects Potential marker	Subjects with OPL are classified as high-risk group (HRG), and CL as low-risk group (LRG	Comparative	Vankadara *et al* (2018)[35]
2	OPL St:14 OML St: 39	PM	NR	Blood	CRP	Potential marker used to gauge premalignant lesions and malignant transformation	HRG: OPL and OML subjects	Comparative	Salema *et al* (2024)[36]
3	POML St: 50 OSCC St: 50 CL St: 50	PM	NR	Blood	NLR/PLR/ HB/ESR	Increased NLR/PLR/HB/ESR levels in OSCC compared to OPL and CL Valuable markers for OPL	HRG: OPL and OSCC subjects LRG: CL subjectsects	Comparative	Ram *et al* (2023)[24]
4	OPL St: 50 CL St: 50	PM	Yes	Blood	NLR	OPL>CL Increased NLR levels in OPL compared to CL Valuable diagnostic adjunct for OPML	HRG: OPL subjects LRG: CL subjects	Prospective case-control	Singh *et al* [40]
5	OPML St: 30 CL St: 30	PM	NR	Blood	WBC/TLC and DLC	OPL>CL Larger sample sizes are required to determine the significance of these markers	HRG: OPL subjects LRG: CL subjects	Prospective	Narang *et al* [38]

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6	OPL St: 100 CL St:100	OL/Lk	NR	Blood	RBC, WBC, Platelets, Hb, Hematocrit	Minimal variations were observed among groups/ Further research is required to claim these as reliable diagnostic markers	HRG: OPL subjects LRG: CL subjects	Randomized trial	Shanthi *et al* [39]
7	OPL St: 50 CL St: OSSC St: 50	PM	NR	Blood	Hb, TLC, DLC	TLC neutrophil count and lymphocyte count showed significant differences among three groups/Used as markers for OPML	HRG: OPL subjects LRG: CL subjects	Case-control	Singh *et al* (2023)[40]
8	OPL St: 14 CL St: 29	PM	Yes	Saliva	NLR	Elevated NLR levels in OPL than CL /Potential prognostic indicator / sensitivity and specificity of 92%ML	HRG: OPL subjects LRG: CL subjects	Prospective	Magdum *et al* (2024)[41]
9	CL St: 60 TU St: 60 TU+OPL St: 60 TU+OML: 60	PM	Yes	Sera	WBC/PLC/ HB/CRP/ESR	WBC, PLC, HB levels were decrease in three groups compared to CL CRP/ESR levels were higher in three groups compared to CL	HRG: TU and OPL subjects MRG: TU and OML LRG: TU and CL	Cross-sectional	Nimbal *et al* [33]

DISCUSSION

Our systematic review based study indicated specific biochemical and haematological indicators that could serve as markers in risk stratification and early detection of OPL. The OPL group exhibited significantly higher levels of biochemical markers IL-6, IL-8, TNF-α, HCC-1, PF-4, FRR, TP, MDA, MMP-12, and Ceruloplasmin and hematological markers NLR, PLR, CRP, ESR, WBC, and low Hb as compared to the control group. Following risk stratification, a group with older age, tobacco association with OPL, and elevated levels of markers were categorised as a higher-risk group. Similar to our study, to determine the potential of biochemical markers in the early detection of OPL, Dikova *et al.*, undertook a 3-year study at the Oncology laboratory of the University General Hospital of Valencia (HGUV) Spain [21]. The study analyzed the panel of cytokines IL-1α, IL-6, IL-8, IP-10, MCP-1, TNF-α and HCC-1, and PF-4 among three groups of TU 33OSCC/33OPL/33CL. The findings suggest that the panel of five markers IL-6, IL-8, TNF-α, HCC-1, and PF-4 discriminate between OSCC OLP and CL and serve a useful role in early disease detection. The results are similar to our study analysis and to a 2-year study carried out by Jureti *et al.*, at the Department of Oral and Maxillofacial Surgery of the University of Rijeka Croatia [30]. The study includes three groups' 19OPML/19OSCC/19CL to determine the levels of proinflammatory cytokines IL-6 and TNFα. Elevated levels of proinflammatory cytokines were found in the OSCC and OPL group as compared to the CL group. To assess the potential of TNF-α, a 3-year experimental study was carried out by Krishnan *et al.*, in dental clinics in Chennai [25]. The study involved 100 OPML and 100 OSCC who consumed tobacco and 100 CL and reported that the proinflammatory cytokine TNF-α marker discriminated the premalignant lesions from malignant ones with higher specificity and sensitivity. The results were similar to a 1-year comparative study by Ameena *et al.*, at Azeezia Dental College of India [28]. TNF-α level was higher in LK and in OSCC who were TU as compared to CL. A P value ≤ 0.01 was found in the TNF-α level between the different histopathological grades of OPL and OSCC. Another comparative study with promising results for LDA as a potential and promising marker for the detection of OPL was undertaken by Javaraiah *et al.*, in the Department of Sagar College of Dental Sciences India to detect the potential of LDA as a biochemical marker in the early detection of OPL [23]. There was a significantly elevated level of LDH in a group of TU with OPL (706.1 ± 1. 99 U/L) as compared to TU without OPL (319 ± 80.53 U/L) and CL (267 ± 27.64 U/L). Our study found that it is necessary to investigate the potential biochemical markers capable of assessing the risk of malignant transformation in OPL. Similarly, López-Jornet *et al.*, conducted a study to evaluate the potential of biochemical markers ADA, FRR and TP [26]. Among study groups, 9. 9% were active smoking TU in the OPL group, whereas 42% of the OPL group and 70% of participants in the CL group had never consumed tobacco. There was no significant difference in ADA levels between the two groups. Though levels of Ferritin (FFR) which plays a key role in cancer progression, (12.66 ± 10.50) and TP (23.41 ± 17) were significantly higher in the OPL group as compared to the CL; FRR (7.19 ± 4.44); TP (14.15 ± 15.19) with sensitivity and specificity of 54.3, indicated FRR and TP as potential markers for OPL [42]. As Matrix Metalloproteinase (MMP) plays a role in the modification of extracellular matrix, a study was conducted by Saleem *et al.*, among TU groups 30OSF/30OSCC/30CL to assess the potential of salivary biochemical MMP-12 marker in precancerous lesions [22]. Higher expression of MMP-12 was observed in oral submucous fibrosis as compared to CL, indicating a noninvasive and early diagnostic marker of OSF. The study reported that MMP-12 expression was higher among a group of TU. To examine the potential of biochemical markers GSH, TP and Serum Albumin (SA) levels in SLT consumers with OPL and malignant lesions, a study was

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undertaken by Nimbal *et al.*, at the Dental College of India. The findings suggest a higher level of GSH and SA in CL as compared to other groups and TP was found as a weak marker as no significant difference was found between groups [33]. To assess the potential of Hematological markers in the early detection of OPL, a comparative study was executed by Vankadara *et al.*, at Dental College and Hospital of India to detect CRP marker of inflammation [35]. The CRP levels were higher in Group 1, ranging from 0. 8 to 53. 9 mg/l with a mean SD of 5.59 ± 9. 86 mg/l compared to CL with CRP levels ranging from 0.1 to 18.3 mg/l with a mean SD of 3. 88 ± 4.50 mg/l considered CRP as a potential marker for assessment of severity of disease. The findings are similar to a study carried out by Salema et al., at Dental College and Hospital of India to assess the potential of CRP markers in the detection of OPL [36]. Another study was carried out by Ram *et al.*, to examine the potential of hematological markers NLR, PLR, HB, and ESR in early detection of precancerous and cancerous oral lesions [24]. The mean NLR was higher in OPL (3.12) and OSCC groups (3.67) as compared to CL (2.16). The mean Hb content was decreased in the OPL (13.77) and OSCC (12.76) group than CL (14. 8). Whereas the ESR was lower in CL (9.65) as compared to OPL (17.2) and OSCC (27.4). These markers can be used for the early detection of OPL and OSCC. A study was undertaken by Nimbal *et al.*, at the Dental College of India to evaluate the potential of hematological markers WBC, PLC, HB, CRP and ESR in TU with premalignant and malignant lesions [33]. According to the findings, CRP, total Red Blood Cell counts (RBC) and ESR levels were significantly higher in TU and OPL groups than in CL group. Whereas the Hb levels, total platelet and leukocyte count, were decreased more in TU and OPL exposed subjects than CL group indicating chronic inflammation and impaired pulmonary function due to TU. The limitations of the systematic review include variations in study designs, risk factors such as tobacco exposure and patient population, and small sample sizes, across studies included. Future research should focus on longitudinal studies with large sample sizes to validate the reliability and efficacy of these markers in risk stratification and early detection of OPL.

CONCLUSIONS

The biochemical and hematological markers in Tobacco users are potential markers in the early detection of OPL from malignant lesions with diagnostic and prognostic significance. The OPL group exhibited significantly higher levels of biochemical markers IL-6, IL-8, TNF-α, HCC-1, PF-4, FRR, TP, MDA, MMP-12 and ceruloplasmin and hematological markers NLR, PLR, CRP, ESR, WBC, and low Hb as compared to the control group. Following risk stratification, a group with older age, tobacco association with OPL, and elevated levels of markers were categorised as a higher-risk group. Integrating these findings into clinical protocols leads to robust assessing methods, ultimately improving patient outcomes.

Authors Contribution

Conceptualization: MRT
Methodology: MM
Formal analysis: SA
Writing, review and editing: MRT, AA[1], MQKG, MAA[2], SAT, SA

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

The authors declare no conflict of interest.

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Systematic Review

Insights into Factors Impacting on Non-Communicable Diseases in the Prisons of Pakistan- A Scoping Review

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ABSTRACT

Non-Communicable Diseases (NCDs) continue to increase globally, including where recorded among prison populations. Pakistan, like many low- and middle-income countries is facing significant health system challenges. Little is known about NCDs in its prison population. A scoping review mapped and described what is known about factors impacting on NCDs in the prison population of Pakistan. **Objective:** To describe factors impacting Non-Communicable Diseases (NCDs) in the prison population of Pakistan and to inform policy and improve prison conditions, nutrition, and healthcare for effective NCD management and care. **Methods:** A comprehensive search was conducted on Web of Science, PubMed and EMBASE, restricted to publications from 2000 to 2023. Eight studies fulfilled the eligibility criteria. Records were independently screened, charted and content analysis was undertaken. **Results:** Six themes were generated; Nutritional and dietary provisions, Physical activity and body mass index; Substance use and dependence; Hypertension and diabetes; Access to medical care and Mental health. Prior and detention related risk and lifestyle factors underpin the chronic ill health of people living in prison. These include prior history of smoking and alcohol use, and situational aspects of prison conditions causing environmental stress, malnutrition and sedentarism. Where reported, hypertension, obesity and depression were high among people in prison. **Conclusions:** Prisons are fundamental to the domestic NCD response. Prisons in Pakistan require dedicated resourcing to improve basic conditions, nutrition and healthcare allocations for all people living in prisons. The review highlights the need for prison-based NCD screening, diagnosis, treatment and care in Pakistan, in close alliance with specialist care in hospitals. Further health research is warranted to examine the effectiveness of NCD policies and practices in place in contemporary prison systems in Pakistan.

INTRODUCTION

Non-Communicable Diseases (NCDs) are increasing globally. The main risk factors for NCDs are smoking, alcohol consumption, unhealthy diet and lack of physical activity. According to the most recent data provided by the World Health Organisation (WHO) NCDs are responsible for the deaths of 41 million individuals each year, which is 71% of the deaths occurring around the world [1]. Despite the fact that NCD risks and progression of disease has an impact on individuals of all nationalities, ages and classes, some striking inequalities exist in the burden of disease, particularly in in low resource countries and in marginalised groups such as people living in prisons [1]. This is due to a variety of lifestyle and environmental factors such as alcohol and tobacco use, sedentary behaviours, consumption of salt and an unhealthy diet, and lack of access to healthcare [2]. NCDs in Pakistan are a rapidly increasing public health challenge with health systems largely unprepared for a robust response [3]. There is a dearth of available prevalence data and identification of relevant NCD risk factors in Pakistan [4]. A recent communication by the WHO in 2018 determining various countries profiles for NCDs showed that NCDs are accountable for 58% of all deaths in Pakistan [5]. Nutritional conditions and cardiovascular diseases were

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cited to be responsible for 35% and 29% of the deaths respectively, followed by cancers (8%), respiratory disorders (5%) and diabetes (3%) [5]. There are over 11.5 million people deprived of their liberty on any given day, a more than 25% increase in prison population since the year 2000 [6, 7]. The WHO has identified that NCDs are one of the biggest threats faced by people living in prisons [8]. Prisons are mandated to uphold the right to health of people deprived of their liberty including access to preventative and curative health care, and are accountable for creating a safe and healthy environment for people deprived of their liberty [9]. The total prison population of Pakistan accounts for 87,712 individuals, including pre-trial detainees (70%), female prisoners (1.6%), minors (1.6%) and foreign prisoners (1.2%) [10]. According to the Federal Ombudsman of Pakistan, the national overcrowding rate in the prison system of 116 prisons is 136.8%, with significantly higher percentages depending on the prison [11]. This leads to insufficient living space, poor or non-existent ventilation, limited sanitation and hygiene facilities, inadequate nutrition, and interrupted medical supplies impacting on the health and lives of people living in prison. Medical facilities tend to be extremely poor in the Pakistan prisons, particularly for women and which contribute to increased mortality rates in the general prison population [12, 13]. Research by Qadir TF *et al.*, in 2017 showed that mental health care services for prisoners, including a follow-up or proper rehabilitation systems are completely lacking in Pakistan [14]. Very little is known about NCDs in the Pakistan prison population. Hence, a scoping review was conducted which maps and describes what is known about factors impacting on NCDs in the prisons of Pakistan.

METHODS

The methodological framework developed by Arksey and O'Malley served as a guide for the scoping review and covered the following key steps: defining the research question; looking for related studies; choosing studies; charting the data; and compiling, summarising, and reporting the findings [15, 16]. The underpinning research question was; what do we know about factors impacting on NCDs in the prisons of Pakistan? The protocol for this scoping review was developed using the PRISMA guidelines for scoping reviews [17]. A comprehensive search was conducted in 2023 on various electronic databases such as Web of Science, PubMed, EMBASE and Google Scholar with no date restriction as shown in table 1.

Table 1: Search Terms

Initial Terms	Related Terms
Prison	Inmates, Jail, Gaol, Incarcerate
Obesity	Obese, Overweight, Body Mass Index, Nutrition, Diet, Nutrition Assessment, Nutrition Surveys, Dietary Behaviour, Fruit Intake
Non Communicable Disease	Cardio-Vascular Disease, Diabetes, Obesity, Smoking Status, Alcohol Consumption, Hypertension, Dietary Salt, Cancer
Physical Activity	Exercise, Physical Inactivity, Sports

Results from the electronic search were downloaded into EndNote software and duplicates were deleted, where possible. All title and abstracts were screened thoroughly to identify records meeting the selection criteria. The exercise was supported by hand searching in the reference list of included records. Eligibility criteria were applied to identify records for inclusion, using the PCC framework as shown in table 2.

Table 2: Eligibility Criteria

PCC Element	Include	Exclude
Prison	Setting: Studies Based on a Prison Setting	Studies Referring to other Population Groups
	Population of Interest: People Living in Prison of All Ages, Any Gender And From Any Majority or Minority Group	
Concept	Outcome: NCD Measured (Cardio-Vascular Disease, Diabetes, Obesity, Smoking Status, Alcohol Consumption, Hypertension, Dietary Salt, Cancer)	Studies That Did Not Report Relevant NCD/ Health Experiences Relating To The Specified Prison Population
Context	Geographical Coverage: Drawing on Primary Data from Studies Focusing on Pakistan	Studies that did not Focus on Pakistan
	Language: Studies Published in English Language	Languages other than English
	Period of Interest: Studies Published from 2000-2023	Published Outside of 2000-2023
Research Type	Type of Studies: All Empirical Peer Reviewed Studies with no Restriction on Methodology (quantitative, Qualitative, Clinical Case or Mixed Method).	Commentaries, Letters to the Editor, Reviews.

Records were independently screened by author one with support from the authorship team. Eight records fulfilled the eligibility criteria and were subsequently charted (author; year of publication; location and setting; study design; sample characteristics; key outcomes) [16]. Data were then analysed using a content analysis approach [18]. All the studies were read thoroughly to familiarise with extant information and supported by a coding exercise of text using a process of selective reduction by generating manageable content categories and subsequent generation of code categories. Figure 1 displayed the PRISMA Flowchart.

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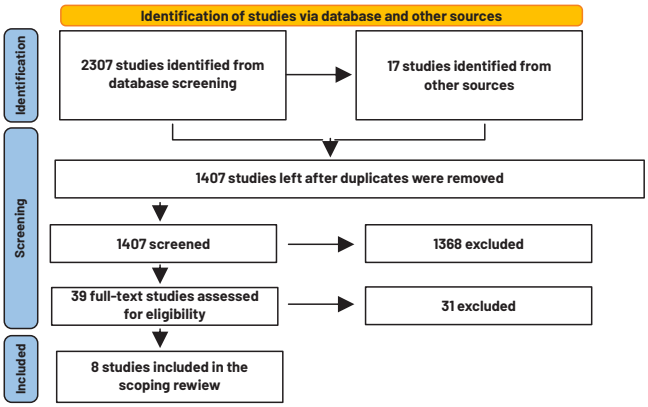

Figure 1: PRISMA Flowchart

RESULTS

All of the studies were published after the year 2005. Authors were commonly from Pakistan. All were cross-sectional studies and investigated NCD risk factors in prison populations located in various urban areas and provinces of Pakistan. Six themes were generated in the content analysis; Nutritional and dietary provisions, Physical activity, and body mass index; Substance use and dependence; Hypertension and diabetes; Access to medical care and Mental health. Prior and detention related risk and lifestyle factors underpin the chronic ill health of people living in prison in Pakistan. These include prior history of smoking and alcohol use, and situational aspects of prison conditions causing environmental stress, malnutrition, and sedentarism. Where reported, hypertension, obesity and depression were high among people in prison. It was included that illustrative quotes from qualitative studies where appropriate as shown in table 3.

Table 3: Charted Records

Study Reference	Study Design	Location of Study	Focus	Type of Participants	Number of Participants	Conclusions (see in text for prevalence data)
(Mukhtar *et al.*, 2013) [19]	Cross-Sectional	Prisons Located in Four Provinces; Sindh, Punjab, Baluchistan and Khyber Pakhtoon Khuwah	Dietary Behaviours of Female Prisoners	Female Prisoners Aged 16 Years and Over	269 Females	High prevalence of NCDs in people living in prison. High incidence of smoking in people living in prison compared to normal population. Poor dietary provisions: low fruit intake and high oil consumption
(Khattak *et al.*, 2008) [20]	Cross-Sectional	Various Female Prisons	Dietary Scales of Female Prisoners and Children	Female Prisoners and Children	Not Mentioned	Insufficient nutritional adequacy in people living in prison
(Qadir *et al.*, 2014). [21]	Cross-Sectional	Karachi Prison	Health and Nutritional Status of Prisoners	Male Prisoners Aged 18-65 Years	433 Males	Inadequate and nutritionally imbalanced diets resulting in the people of prison developing nutritional deficiencies. People living in prison malnourished and underweight. Common use of substances by people living in prison
(Manzoor *et al.*, 2022) [22]	Analytical Cross-Sectional	Kot Lakhpat Prison in Punjab	Gender Differences in Health Status of Prisoners	Male and female Prisoners	320 Prisoners	High frequencies of hypertension. High rates of depression and anxiety
(Hafizullah *et al.*, 2014) [23]	Cross-Sectional	Central Prison in Peshawar	Peshawar Heart Study (PHS) to Identify Risk Factors for Cardio-Vascular Disease	Male and female Prisoners	166 Prisoners	Lack of physical activity and sedentary lifestyles in people living in prison. Frequent smoking and high rates of obesity and hypertension
(Jat *et al.*, 2020) [24]	Descriptive Cross-Sectional	Malir and Central Jails in Karachi	Substance and Tobacco use by Prisoners	Male Prisoners Aged 18-65 Years	600 Males	High prevalence of substance abuse in people living in prison
(Shahid *et al.*, 2014) [25]	Cross-Sectional	District Jail in Lahore	Mental Health Status of Prisoners	Male Prisoners	100 Males	High rates of depression in people living in prison
(Khan *et al.*, 2012) [26]	Cross-Sectional	Central Prison in Peshawar	Prevalence of Depression of Prisoners	Female Prisoners	64 Females	High frequencies of depression and high incidence of smoking observed in people living in prison

Nutritional and dietary provisions

Four studies revealed various nutritional deficits in provisions allocated by prison systems. A study analysing the dietary behaviours of women living in prison in four different provinces in Pakistan showed that approximately 76% of the females living in prison had no access to any fruits in a week whilst 17% received 1-3 servings of fruit and 7% received 5 or more servings a week [19]. Of note was

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that most women that had access to fruit in various prisons of Pakistan were foreign nationals from Nigeria, Guinea, India, Bangladesh and Thailand [19]. Women and children appeared to be particularly disadvantaged in another study on various prisons in Pakistan, by the general provision of food consisting of pulses and cereals, and the lack of allocation for children [20]. When fruits and vegetables were provided, these were seasonal and locally available [20]. A cross-sectional study performed in the Central jail of Peshawar found that out of the 166 interviewed people living in prison, it was recorded that:"About 83 (50%) were consuming largely vegetables in access of 1400 grams a day. No fruit intake was reported in their meals by 98 (59%) prisoners" [23]. In Karachi prison, nutritional deficiencies in males and lack of satisfaction with quality of food were also identified [21]. Detailed food patterns analysed by Fawad A *et al.*, revealed that 77.5 % of the prisoners in the Peshawar Central prison were consuming 50 to 500 grams of meat on a regular basis and with 12% consuming more than 500 grams of meat [23].

Physical activity and body mass index (BMI)

Several studies assessed physical activity, BMI and changes in weight of people living in prisons. Males living in Karachi prison reported rates of high sedentarism. Only 9% reported that they: "Exercised regularly and went to the gym located within the prison on a regular basis." 13.16% stated that they "exercised but not on a regular basis." [21]. Both genders living in the Central Prison of Peshawar also reported lack of physical activity with 71.7% indicating they had no regular exercise schedule [23]. A survey performed to investigate BMI amongst women living in selected prisons across the various provinces in Pakistan showed that the mean BMI of these women (n=269) was 26.63 (the normal BMI range is 19-24.9) [19]. This study also reported that 46.5% had a normal BMI, while 26.4% and 27.13% were reported to be overweight (BMI = 25-29.9) and obese (BMI > 30), respectively. A different study by Fawad A *et al.*, revealed similar findings among males showing an average BMI of 26.52, with 52% having a BMI higher than 25, 35% categorised as overweight and 23.5% were regarded as obese [23]. Qadir M *et al.*, reported on a 0.9% increase in malnourishment from the point of committal to the time of study [21]. Those classified as underweight also increased by 17.5% and 37% experienced weight loss [21].

Substance Use and Dependence

The majority of included studies described the levels of substance use behaviours (alcohol, tobacco and drugs) during their time in prison. A study of 320 people living in the Kot Lakhpat prison of Lahore showed that 5.3% of both genders reported experience of consuming alcohol [22]. Amongst a sample of 269 women living in prison in various provinces of Pakistan, 24.9% were categorized as current smokers and the youngest age at which they started smoking was found to be 10 years [19]. Individuals that had reported to be smoking daily were further categorised as consuming 1-4 cigarettes daily (18%), 5-10 cigarettes daily (49%), 11-15 cigarettes daily (12%), 15-20 cigarettes daily (16%) and more than 20 cigarettes daily (5%). Most women were observed to smoke manufactured cigarettes (87.5%) whilst the rest smoked homemade cigarettes (such as biiri and huqqa) (12.5%) [19]. A study focusing on 433 males living in Karachi prison revealed high rates of smoking with 68.67% reported to be smokers [21]. High rates of smoking were documented in both genders of people living in the Central prison of Kot Lakhpat Lahore; where 320 people living in prison (29.7%) were smokers [22]. Similar results were shown in the Central Prison of Peshawar where 21.7% of the interviewed males were found to be active smokers [23]. In the same prison, 60.1% of women smoked cigarettes (n-= 140) and 28.1% smoked 1-5 cigarettes every day, 17.2% smoked 6-10 cigarettes daily, 15.6% smoked 10-15 cigarettes daily [26]. Drug use and dependence was also investigated but was relatively low. A study of 433 males living in Karachi prison reported that a combination of street drugs (naswar, pan, gutka and manpuri) were used by 18.71% [21]. 5.77% were dependent on drugs like heroin, cannabis ("ganja"), hashish ("charas") and opium [21]. Women living in the Central Prison of Peshawar were interviewed and 93.7% had not used any drug [26]. In the Kot Lakhput prison of Lahore, 9.1% of people living in prison reported drug dependence (72.4% were male) [22]. A study of 166 people living in Peshawar Central Prison revealed that 28.3% (47 prisoners) were addicted to snuff ("naswar"). In Malir Prison of Karachi 23.3% of people living in the prison reported substance use, with 90% reporting various of routes to administration; 8% reported injecting drug use [24]. Moreover, heroin (52%) was found to be the most popular among prisoners followed by crystal meth (17%), cannabis (15%), synthetic substances (8%), ice (5%), opioid (1%) and other substances (2%) [24].

Hypertension and Diabetes

In Karachi prison, Qudir M *et al.*, reported that 87 people were found to be hypertensive, with 29 suffering from diabetes and hypertension [21]. Males and females living in the Central Prison at Kot Lakhpat Lahore reported that hypertension was the most common NCD, with 26.25% identified as hypertensive [22]. A cross sectional study carried out in the prison of Peshawar involving 166 male and female prisoners showed that the mean diastolic BP was 87.7 mmHg and the mean systolic BP was 136.8 mmHg. Moreover, it was reported: "34.33% had systolic BP more than 140 mmHg while 61.44% had diastolic BP more than 90 mmHg" and met the criteria for hypertension [23]. The study additionally tested the blood cholesterol level and documented that 37.95% of the prison population had cholesterol levels higher than 180 mg/dl, with a mean cholesterol of 178.9 mg/dl. Mean blood sugar level was noted to be 135 mg/dl and 2% were found to have a blood

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sugar level of more than 180 mg/dl [23].

Access to Medical Care

Only one study assessed levels of access to healthcare. Manzoor I *et al.*, described medical facility provisions in the Central Prison at Kot Lakhpat Lahore [22]. Despite having a doctor and a medical centre in the prison, only 77.2% of people living in the prison reported having access to medical facilities, 56.3% reported regular check-ups and 61.9% obtained essential medication.

Mental Health

Although mental illness was not specifically searched for as part of this review, a number of included studies also reported on prevalence of mental health conditions among people living in prisons in Pakistan. A study by Shahid I *et al.*, examined the prevalence of depression, stress and anxiety in the male prison population (n= 100) in the District Prison of Lahore [25]. Prevalence of depression was found to be 85%, according to the Beck Depression Inventory (BDI) scale. 35% suffered from severe depression, 20% were reported to be suffering from moderate depression and 30% experienced mild depression. Those with a history of childhood sexual abuse (BDI= 48) and substance abuse (BDI= 29) had a higher BDI score compared to those with no history of childhood sexual abuse (BDI= 20) and substance abuse (BDI= 14). Moreover, the co-morbid presence of NCDs, such as heart disease, diabetes and hypertension etc raised the BDI score level from 21 to 36 [25]. A study in the Central Prison of Kot Lakhpat Lahore also reported on the mental health profiles of the prison population, and stated that: "Out of 320 prisoners, 50% were depressed, 62.2% reported an anxiety state, and 43.1% had mood tantrums." [22]. Fawad A *et al.*, in their study referred specifically to women, and highlighted that those who were married, middle aged and from a low socioeconomic background were at a higher risk of being depressed compared to others [23].

DISCUSSION

The review maps and describes what is currently known about NCDs in the Pakistan prison population and health factors related to conditions of detention. Included records show that rates of NCDs are high in prison populations in Pakistan and that there is also a high prevalence of risk factors such as overweight and obesity, poor diet, hypertension and a history of substance use. Despite the vulnerabilities of the prison population in Pakistan, the only study examining access to medical services suggests that this is very poor, thus compounding the adverse impact of an overcrowded prison environment on people's health. People living in prison are disproportionately impacted by poverty, ill-health, prior traumas, stigma and discrimination [6-8]. It was speculated that vulnerability to risk of NCD development (for example diabetes, hypertension, mental health disorders) in prison populations in Pakistan could potentially be due to prior exposure to poverty, marginalisation and stigmatisation and prior unhealthy lifestyle behaviours (for example substance use, obesity and overweight) of people in conflict with the law, and exacerbated by the conditions of detention (poor quality and inadequate nutrition, inability to exercise, high levels of stress). Dietary behaviours are one of the leading risk factors of NCDs [27]. Severe forms of malnutrition are linked with increased risk of developing cardiometabolic NCDs [28]. This is especially pertinent to the adequacy of food provisions in Pakistan prisons. In high income countries, provision of adequate and balanced nutrition for imprisoned people appears more common, than in low resource setting. For example, Edwards JS *et al.*, examined the diet of prisoners in England and revealed that prison populations were able to choose a nutritionally balanced diet, with an exception of some nutrients [29]. Additionally, the service of food in the prisons of Australia was evaluated by Williams P *et al.*, and it was found that people living in prison were receiving an acceptable variety of food that met most nutritional requirements [30]. Several studies in this review indicate the need for increased resourcing of prison health budgets in Pakistan to include greater variety of nutritious food, including a specific allocation for all women and children living in prison. Providing a nutritionally healthy and well-balanced diet is vital in prisons in Pakistan, and interventions to design menus according to the Recommended Daily Allowance (RDA) should be operationalized [21]. One study illustrates the complexities of maintaining a healthy weight in prison in Pakistan [23]. Being obese or overweight is associated as one of the main risk factors of increasing NCDs worldwide [31]. Obesity is also linked with progressively more sedentary lifestyle and increased consumption of oil in meals [32]. The review also points to concerning levels of substance use and dependence, but also unaddressed high rates of mental health symptoms and disorders in Pakistan's prisons. Depression in particular appears high in the prisons of Pakistan. Globally, cardio-vascular diseases have been reported to be one of the biggest cause for increasing mortality in prisons, above substance abuse and mental health [32-34]. There is a link between cigarette smoking and mental health issues such as depression, panic and anxiety disorder [35, 36]. Alcohol consumption has been associated with increased suicide inside prisons [37, 38]. In the United Kingdom, Steadman HJ *et al.*, reported on relatively low rates of depression among females living in prison, particularly when compared to levels documented among Pakistani female in prison [39]. A possible explanation for this is the potentially better prison environment in the United Kingdom and the accessibility to appropriate health care in prisons. Authors in a number of studies have suggested culturally

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appropriate interventions such regular prayers and recitation of the Holy Qur'an to help with depression and stress [23]. Shahid I *et al.*, added that successful measures such as musical therapy proposed by Gold C *et al.*, could also be adopted in Pakistan to help reduce mental health issues and risks of suicide in prisons [25, 40]. Access to healthcare is a basic right for those living in prison. Prisons in low resource settings such as in Pakistan generally struggle with resourcing of the health response. The WHO advises screening individuals for the risk factors of NCDs, on their arrival to prison in order to detect any early signs of poor nutrition and well-being, harmful alcohol and substance use, smoking and sedentary behaviours [41]. It underscores that it is important that people in prison go through these detailed health and well-being assessments to recognise all of their physical and mental health needs so appropriate medication and facilities can be provided to this population [41, 42]. Given the lack of detection of NCDs in prison populations in Pakistan it is vital to have up to date facilities along with regular medical check-ups and screening of all persons to screen and detect any NCDs at an initial stage so that treatments can be started immediately. This is especially the case for women who do not experience equal access to healthcare in prison in Pakistan [43]. This scoping review was conducted systematically following published guidelines and is the first to focus on documenting extant literature and understanding of NCDs in the Pakistan prison system. Limitations center on the restriction on the English language, thereby potentially missing Urdu records. Scoping reviews also do not include a quality assessment of methodology of included records.

CONCLUSIONS

The scoping review highlights the need for national surveillance and monitoring of NCDs to include prison settings in Pakistan. Efforts to improve standards of care and environmental conditions of detention, including access to basic needs provisions (i.e. food, NCD drugs), opportunity to exercise and access recreational areas inside prisons, and access healthcare (including mental healthcare) in prison can assist in supporting people living in prison, and ultimately inhibit progression of concerning rates of NCD related chronic ill-health. Prisons in Pakistan require dedicated resourcing to improve basic conditions, nutrition and healthcare allocations for all people living in prisons. Further prison health research is warranted to examine the effectiveness of NCD policies and practices in place in prison systems to improve the health and well-being of the prison population of Pakistan. Decongestion measures could include greater application of non-custodial (or alternative) community sentencing measures.

Authors Contribution

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Methodology: TS, MCVH, EP
Formal analysis: TS, MCVH, EP
Writing, review and editing: TS, MCVH, EP

All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

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